EFFICACY AND MECHANISM EVALUATION

VOLUME 3 ISSUE 7 AUGUST 2016
ISSN 2050-4365

Does metformin reduce excess birthweight in offspring of obese pregnant women? A randomised controlled trial of efficacy, exploration of mechanisms and evaluation of other pregnancy complications

Carolyn A Chiswick, Rebecca M Reynolds, Fiona C Denison, Amanda J Drake, Shareen Forbes, David E Newby, Brian R Walker, Siobhan Quenby, Susan Wray, Andrew Weeks, Hany Lashen, Aryelly Rodriguez, Gordon D Murray, Sonia Whyte, Ruth Andrew, Natalie Homer, Scott Semple, Calum Gray, Marian C Aldhous, Karen Noble, Sarah Cunningham-Burley, Alice Keely and Jane E Norman

DOI 10.3310/eme03070

National Institute for Health Research

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Declared competing interests of authors: Jane E Norman has received research grants from government and charitable bodies for research into pregnancy problems, including a grant from the charity Tommy's to address the adverse consequences of maternal obesity in pregnancy. Jane E Norman's institution receives funding from GlaxoSmithKline for Jane E Norman's participation in a Data Monitoring Committee for a study on preterm birth. Jane E Norman and Gordon D Murray have both served on the Efficacy and Mechanism Evaluation Board during the lifetime of this project. Jane E Norman is a member of the Health Technology Assessment Maternal Newborn and Child Health prioritisation panel.

Published August 2016
DOI: 10.3310/eme03070

This report should be referenced as follows:

Chiswick CA, Reynolds RM, Denison FC, Drake AJ, Forbes S, Newby DE, *et al*. Does metformin reduce excess birthweight in offspring of obese pregnant women? A randomised controlled trial of efficacy, exploration of mechanisms and evaluation of other pregnancy complications. *Efficacy Mech Eval* 2016;**3**(7).

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

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This report

The research reported in this issue of the journal was funded by the EME programme as project number 08/246/09. The contractual start date was in November 2014. The final report began editorial review in July 2015 and was accepted for publication in April 2016. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Does metformin reduce excess birthweight in offspring of obese pregnant women? A randomised controlled trial of efficacy, exploration of mechanisms and evaluation of other pregnancy complications

Carolyn A Chiswick,[1] Rebecca M Reynolds,[2] Fiona C Denison,[1] Amanda J Drake,[2] Shareen Forbes,[2] David E Newby,[2] Brian R Walker,[2] Siobhan Quenby,[3] Susan Wray,[4] Andrew Weeks,[5] Hany Lashen,[6] Aryelly Rodriguez,[7] Gordon D Murray,[7] Sonia Whyte,[1] Ruth Andrew,[2] Natalie Homer,[2] Scott Semple,[8] Calum Gray,[8] Marian C Aldhous,[1] Karen Noble,[9] Sarah Cunningham-Burley,[7] Alice Keely[1] and Jane E Norman[1]*

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Background: Maternal obesity is associated with high birthweight, obesity and premature mortality in adult offspring, probably as a result of maternal hyperglycaemia and insulin resistance. We present the results of a trial designed to test the hypothesis that metformin will improve insulin sensitivity in obese pregnant women, thereby reducing the incidence of high-birthweight babies.

Objective: To determine the efficacy of metformin (up to 2500 mg daily) given to obese pregnant women in reducing the gestational age-, parity- and sex-adjusted birthweight centile of the baby.

Design: Double-blind, placebo-controlled, randomised controlled trial with embedded substudies.

Setting: Fifteen NHS hospitals in the UK.

Participants: Pregnant women aged ≥ 16 years with a singleton fetus and a body mass index of ≥ 30 kg/m^2.

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Intervention: Metformin tablets (or placebo) administered between 12 and 16 weeks' gestation until delivery of the baby.

Main outcome measures: The primary outcome measure was z-score corresponding to the gestational age-, parity- and sex-adjusted birthweight centile of live-born babies delivered at ≥ 24 weeks' gestation. The main secondary outcome was maternal insulin resistance at 36 weeks' gestation. Embedded substudies were included to assess the effect of metformin on insulin sensitivity using the hyperinsulinaemic–euglycaemic clamp; endothelial function; maternal and fetal fat distribution using magnetic resonance imaging; placental expression of 11β-hydroxysteroid dehydrogenase types 1 and 2 and glucocorticoid receptor; and myometrial contractility and glycogen storage.

Results: We randomised 449 women to either placebo ($n = 223$) or metformin ($n = 226$), of whom 434 were included in the final intention-to-treat analysis. Mean birthweight at delivery was 3463 g [standard deviation (SD) 660 g] in the placebo group and 3462 g (SD 548 g) in the metformin group. The estimated effect size of metformin on the primary outcome was non-significant [adjusted mean difference in z-score –0.029, 95% confidence interval (CI) –0.217 to 0.158; $p = 0.7597$]. There was no evidence of a reduction in the main secondary outcome of homeostatic model assessment – insulin resistance (HOMA-IR) at 36 weeks' gestation (mean HOMA-IR 5.98 and 6.30 molar units in the placebo and metformin groups, respectively; adjusted mean ratio 0.974, 95% CI 0.865 to 1.097). Metformin had no effect on the combined adverse outcome of miscarriage, termination of pregnancy, stillbirth or neonatal death. Subjects taking metformin demonstrated increased insulin sensitivity [glucose disposal per unit plasma insulin difference between means during high-dose insulin 0.02 mg/kg, 95% CI 0.001 to 0.03 mg/kg (fat-free mass)/minute/μIU/l; $p = 0.04$] compared with those taking placebo and enhanced endogenous glucose production [difference between means 0.54 mg/kg, 95% CI 0.08 to 1.00 mg/kg (fat-free mass)/minute; $p = 0.02$]. There were no differences in endothelial function, maternal or fetal body fat distribution, placental expression of 11β-hydroxysteroid dehydrogenase types 1 and 2 and glucocorticoid receptor, or myometrial contractility and glycogen storage.

Conclusions: Metformin has no clinically significant effect on birthweight centile in obese pregnant women. Follow-up studies of the children born to participants in the trial are required to determine whether or not there are any longer-term benefits or harms of maternal metformin for offspring weight, fat mass or metabolism.

Trial registration: Current Controlled Trials ISRCTN51279843.

Funding: This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership.

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List of abbreviations

ADP	air displacement plethysmography
ANOVA	analysis of variance
AUC	area under the curve
BMI	body mass index
cDNA	complementary deoxyribonucleic acid
CI	confidence interval
CRP	C-reactive protein
CV	coefficient of variation
DNA	deoxyribonucleic acid
EGP	endogenous glucose production
ELISA	enzyme-linked immunosorbent assay
EMPOWaR	Efficacy of Metformin in Pregnant Obese Women, a Randomised controlled trial
FFM	fat-free mass
FLASH	fast low-angle shot
FMD	flow-mediated dilatation
GDM	gestational diabetes mellitus
GR	glucocorticoid receptor
GTN	nitroglycerin
HDL	high-density lipoprotein
HOMA-IR	homeostatic model assessment – insulin resistance
HPA	hypothalamic–pituitary–adrenal
HSD	hydroxysteroid dehydrogenase
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
IL	interleukin
ITT	intention to treat
LDL	low-density lipoprotein
LGA	large for gestational age
LiP	Lifestyle in Pregnancy
M/I	glucose disposal per unit plasma insulin
MOP	Metformin in Obese Pregnancy
MRC	Medical Research Council
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRS	magnetic resonance spectroscopy
NEFA	non-esterified fatty acid
OR	odds ratio
PAI	plasminogen activator inhibitor
PCOS	polycystic ovary syndrome
PSS	physiological saline
PSS 0-glucose	physiological saline lacking glucose
Ra	rate of appearance
RCT	randomised controlled trial
Rd	rate of disappearance
RNA	ribonucleic acid
RT	reverse transcriptase
SAE	serious adverse event
SD	standard deviation
SOP	standard operating procedure
UPBEAT	UK Pregnancies Better Eating and Activity Trial
v/v	volume per volume
WGD	whole-body glucose disposal
WHO	World Health Organization

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Plain English summary

Obesity during pregnancy is common. This is of concern because obese women have an increased risk of complications including diabetes mellitus and pre-eclampsia. There is also an increased risk for their babies to be born larger than average or to be stillborn. In addition, there may be harmful effects of maternal obesity that persist into the baby's adult life, including a higher risk of obesity and premature death.

We do not know how obesity causes these problems. We do know that obese pregnant women have higher blood glucose levels and respond less well to the hormone insulin than lean pregnant women, that is, they are 'insulin resistant'. This means that the food supply to the baby is potentially too great, leading to a high birthweight. The link between insulin resistance and high birthweight has already been demonstrated, as has a link between high blood glucose and greater risk of pregnancy problems.

The aim of this study was to see whether or not giving obese pregnant women a drug called metformin reduced the risk of them having a larger than average baby. Metformin is safe to take during pregnancy and works by reducing insulin resistance.

We recruited 449 women to take part in the study. They were randomly assigned to receive treatment with either metformin or placebo tablets during their pregnancy.

The average birthweight of babies born to women in both groups was similar: 3463 g in the placebo group and 3462 g in the metformin group. There was no increased risk of a bad outcome in either of the groups with the exception of nausea and vomiting, which were more common in the metformin group. We also looked at whether or not metformin affected how the body handles glucose, the size of the baby's liver and contractions of the muscle tissue of the womb. We found that metformin does affect how the body handles glucose, but there was no effect on liver size or on womb contractions.

We can conclude that metformin is not an effective treatment for obese pregnant women to reduce the risk of having a larger than average baby.

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Scientific summary

Background

Rates of obesity, as defined by a body mass index (BMI) of > 30 kg/m^2, have risen alarmingly in recent decades. Around 20% of women booking for antenatal care in the UK are obese. The adverse effects of maternal obesity on pregnancy complications for both the mother and the fetus are well established and there is mounting evidence of a detrimental effect on the longer-term health of offspring. Increasingly, data suggest that maternal obesity may programme offspring later-life obesity, with high birthweight being a marker for increased risk.

The mechanism by which maternal obesity causes excessive neonatal birthweight is not clearly understood but considerable evidence implicates insulin resistance and/or hyperglycaemia. Obese pregnant women are more insulin resistant and hyperglycaemic than their lean counterparts. This enhances nutrient availability for the fetus with consequent excessive growth. There is a strong correlation between the degree of insulin resistance in late pregnancy and both birthweight and fat-free mass at birth. The Hyperglycaemia and Adverse Pregnancy Outcomes study confirms that there is a linear relationship between hyperglycaemia and birthweight, even at glucose levels considered normal during pregnancy. Finally, treating hyperglycaemia in women with confirmed gestational diabetes mellitus (GDM) reduces the incidence of large-for-gestational-age babies and other perinatal complications.

The aim of this trial was to see whether or not giving the insulin-sensitising agent metformin to obese pregnant women between 12 and 16 weeks' gestation until delivery might reduce the future life risk of obesity and metabolic syndrome in the baby. We used birthweight centile as a surrogate marker for future life events as its predictive value has been shown in large epidemiological studies.

Objectives

The primary objective was to determine the efficacy of metformin (up to 2500 mg per day) given to obese pregnant women from 12–16 weeks' gestation until delivery in reducing the gestational age-, parity- and sex-adjusted birthweight centile of the baby.

The secondary objectives were to determine the pattern of association between insulin resistance and adverse pregnancy outcomes, including incidence of pregnancy-induced hypertension, pre-eclampsia, caesarean section and post-partum haemorrhage, maternal weight gain during pregnancy and incidence of the baby's admission to the neonatal unit; to determine the effect of metformin on maternal and neonatal body composition; to determine the effect of metformin on maternal and neonatal inflammatory and metabolic variables (measured at 28 and 36 weeks' gestation and in umbilical cord blood); to confirm that metformin does not increase the rate of babies born with a low birthweight centile; and to determine the efficacy of metformin when analysis was restricted to those with detectable circulating levels of the drug.

A series of nested substudies were included to determine the effect of metformin in obese pregnant women on the maternal hypothalamic–pituitary–adrenal axis; hepatic and peripheral insulin sensitivity at 36 weeks' gestation; endothelium-dependent flow-mediated dilatation; subcutaneous and visceral adipose tissue deposition and hepatic and skeletal muscle ectopic fat distribution; and myometrial contractility and glycogen storage.

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Design

This was a double-blind, randomised, placebo-controlled trial.

Setting

Participants were recruited from 15 UK NHS hospital antenatal clinics between February 2011 and January 2014.

Participants

Caucasian women aged > 16 years and with a BMI of ≥ 30 kg/m^2 and a viable singleton pregnancy between 12^{+0} and 16^{+0} weeks' (+ days) gestation were considered eligible.

We excluded women with pre-existing diabetes mellitus; GDM in a previous pregnancy; systemic disease at the time of trial entry (requiring regular medication or treatment with systemic corticosteroids in the last 3 months); GDM diagnosed in the index pregnancy prior to randomisation; previous delivery of a baby before 32 weeks' gestation; known hypersensitivity to metformin hydrochloride or any of the excipients; known liver or renal failure; acute conditions at the time of trial entry with the potential to alter renal function; lactation; and multiple pregnancy.

Intervention

Metformin tablets (or matched placebo) (500 mg) were administered from as soon as practicable after the point of randomisation (and certainly between 12 and 16 weeks' gestation) until delivery of the baby. The dose regimen was as follows: one tablet per day, escalating by one tablet per day each week over 5 weeks to reach a maximum treatment dose of five tablets per day (2500 mg).

Randomisation and blinding

Treatment allocation concealment was ensured by participant randomisation in a 1 : 1 ratio through a web-based interface provided by the Edinburgh Clinical Trials Unit and stratified by both study centre and BMI band (30–39 kg/m^2 or ≥ 40 kg/m^2). The randomisation sequence was generated by computer and the block size varied randomly between two and four.

Participants, caregivers and study personnel were blinded to treatment assignment until data collection was complete and the database locked. Members of an independent Data Monitoring Committee had access to unblinded data but no contact with study participants.

Main outcome measures

The primary outcome was z-score corresponding to the gestational age-, parity- and sex-adjusted birthweight centile of the live-born babies delivered at ≥ 24 weeks' gestation. The main secondary outcome measure was maternal insulin resistance at 36 weeks' gestation. Other secondary outcomes were maternal fasting glucose and insulin levels and 2-hour glucose level at 36 weeks' gestation; maternal and baby anthropometry and body composition; maternal inflammatory and metabolic indices at 36 weeks' gestation including C-reactive protein (CRP), cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, interleukin (IL) 6, leptin, serum cortisol, non-esterified fatty acids and ratio of plasminogen

activator inhibitor-1 and -2; incidence of low birthweight centile (< 3rd and < 10th); incidence of other adverse maternal and neonatal outcomes including maternal symptoms; maternal plasma concentration of metformin to explore adherence; and the maternal metabolic and inflammatory variables at 28 weeks' gestation.

Methods

Women identified as potential participants were seen for an initial screening visit between 10^{+0} and 16^{+0} weeks' gestation. Written informed consent was obtained. Demographics, a medical history and maternal anthropometry were recorded at baseline. A 75-g oral glucose tolerance test was performed and blood was taken to check liver and renal function. A further fasting blood sample was taken for measurement of inflammatory and metabolic indices. Subjects with normal liver and renal function and glucose tolerance were randomised to receive treatment with metformin or placebo. Participants were reviewed either face to face or by telephone at 18–20, 28, 36 and 40 weeks' gestation, around the time of delivery and 3 months postnatally. Pregnancy complications were recorded and women were asked to complete a side effect questionnaire at each visit. Maternal anthropometry was repeated at 36 weeks' gestation and 3 months postnatally. The glucose tolerance test was repeated at 28 and 36 weeks' gestation and blood was stored for measurement of inflammatory and metabolic indices at these times. The protocol recommended that women who developed GDM be treated with insulin while maintaining their study treatment and blinding. Babies' weight and anthropometry were recorded at birth and 3 months of age.

Substudies

In addition to the above, a subgroup of participants took part in nested substudies.

Maternal hypothalamic–pituitary–adrenal axis

Diurnal cortisol samples were measured in saliva samples collected at baseline and 28 and 36 weeks' gestation. Saliva was collected at bedtime and on waking. Samples were stored at –80 °C. Cortisol was measured by enzyme-linked immunosorbent assay. Placental biopsies were taken from consenting participants and analysed for placental glucocorticoid receptor (GR) and 11β-hydroxysteroid dehydrogenase (HSD) type 1 and 2 messenger ribonucleic acid levels.

Body composition

Maternal fat mass was measured using air displacement plethysmography at baseline, 36 weeks' gestation and 3 months post partum. Neonatal fat mass was measured using the same technique within 72 hours of birth and at 3 months of age.

Hyperinsulinaemic–euglycaemic clamp

Consenting participants who were adherent to treatment underwent a hyperinsulinaemic–euglycaemic clamp at 36 weeks' gestation to characterise the relative effects of metformin on hepatic and peripheral insulin sensitivity.

Endothelial function

Endothelium-dependent flow-mediated dilatation was measured at baseline and at 36 weeks' gestation. Change in diameter of the brachial artery following a flow stimulus created by arterial occlusion was measured using ultrasound imaging.

Magnetic resonance imaging and spectroscopy

Participants were scanned at 28 and 36 weeks' gestation using a Siemens MAGNETOM® Verio 3-tesla magnetic resonance imaging system (Siemens AG, Healthcare Sector, Erlangen, Germany). T1-weighted acquisitions were used to measure maternal subcutaneous and visceral fat, fetal liver volume and fetal subcutaneous fat. Hepatic and skeletal muscle lipid content was measured using ^{1}H-magnetic resonance spectroscopy.

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Myometrial biopsy

A biopsy of the lower segment myometrium was obtained from consenting participants who were delivered by caesarean section. The biopsies were divided, with one portion placed in physiological saline for contractility studies and the other snap frozen for glycogen storage measurements.

Results

In total, 449 participants were randomised, 223 to placebo and 226 to metformin. Of these, two participants withdrew before receiving their treatment allocation. Following allocation of treatment, a further three participants withdrew and one was lost to follow-up. Birth outcome was available for all of the remaining women. Three women (two in the placebo group and one in the metformin group) underwent termination of pregnancy for fetal abnormality, four women miscarried before 24 weeks' gestation and two had a stillbirth, and hence their data were not used for the primary analysis of the primary outcome. Birthweight centiles for the babies of the remaining 434 participants were used in the intention-to-treat (ITT) analysis of the primary outcome.

Mean [standard deviation (SD)] birthweight was 3463 g (660 g) in the placebo group and 3462 g (548 g) in the metformin group. The primary outcome (z-score of birthweight centile for live-born babies of $\geq$ 24 weeks' gestation, adjusted for sex, parity and gestation at delivery) was similar in the placebo and metformin groups [ITT analysis: adjusted mean difference –0.029, 95% confidence interval (CI) –0.217 to 0.158, $p = 0.7597$; per-protocol analysis: adjusted mean difference 0.068, 95% CI –0.188 to 0.324, $p = 0.6001$].

There was no evidence of an effect on our main secondary outcome of homeostatic model assessment – insulin resistance (HOMA-IR) at 36 weeks' gestation – with a mean HOMA-IR in the placebo and metformin groups of 5.98 and 6.30 molar units, respectively (adjusted mean ratio 0.974, 95% CI 0.865 to 1.097). In addition, there was no evidence of an effect on the fasting or 2-hour glucose level (after a 75-g oral glucose challenge) or fasting insulin level at 36 weeks' gestation. In contrast, fasting glucose and the HOMA-IR score at 28 weeks' gestation were lower in the metformin group (adjusted mean difference/ratio –0.105, 95% CI –0.193 to 0.016 mmol/l and 0.895, 95% CI 0.803 to 0.998 molar units, respectively).

Metformin had no effect on maternal weight gain in pregnancy or the neonatal ponderal index. The proportion of live-born babies weighing > 90th centile was similar in the two groups.

Serum IL-6 and CRP concentrations were lower in the metformin-treated group but all other inflammatory and metabolic variables at 36 weeks' gestation and the umbilical cord blood variables were similar in the two groups. Metformin did not appear to prevent the development of GDM.

Diarrhoea and vomiting were significantly more common in the metformin-treated group. The incidence of other adverse outcomes, including preterm birth and low birthweight, caesarean section and post-partum haemorrhage, was similar in the two groups. There were no adverse effects of metformin detected on post hoc safety analyses comparing the proportion of women with a recordable serious adverse event in the two groups or the combined adverse outcomes of miscarriage, termination of pregnancy, stillbirth or neonatal death.

From completed diary entries and analysis using predefined criteria, 118 out of 177 (67%) in the placebo group and 109 out of 167 (65%) in the metformin group were deemed compliant with the treatment. Subsequent analysis of metformin levels showed that detectable levels of metformin were present in the blood of 80 out of 131 (61%) women in the metformin group who gave a blood sample at 36 weeks' gestation.

Substudy results

Maternal hypothalamic–pituitary–adrenal axis

There was no difference in diurnal salivary cortisol levels, or in the increment on waking, between the metformin group and the placebo group. There was also no difference in placental expression of GR, 11β-HSD1 or 11β-HSD2 after adjustment for mode of delivery.

Body composition

There were no differences between the two groups in maternal fat mass measured using air displacement plethysmography at baseline, 36 weeks' gestation and 3 months post-partum. Neonatal fat mass was also the same in the two groups at birth and at 3 months of age.

Hyperinsulinaemic–euglycaemic clamp

Subjects taking metformin demonstrated greater insulin sensitivity than with those taking placebo. The rate of disappearance of glucose was also enhanced in the metformin-treated group. However, endogenous glucose production was higher in the metformin-treated subjects, suggesting that, if anything, those on metformin exhibit a reduced ability to suppress hepatic glucose production in response to insulin.
The lipolytic pathway was equally sensitive to exogenous insulin in both the metformin group and the placebo group.

Endothelial function

All participants exhibited a decline in endothelium-dependent flow-mediated dilatation between baseline and 36 weeks' gestation but there were no differences between the treatment groups. There was no change in endothelium-independent dilatation by treatment group or gestation.

Magnetic resonance imaging and spectroscopy

All participants lost subcutaneous fat mass between 28 and 36 weeks' gestation. However, there was no difference in the percentage change between the treatment groups. There were no differences in visceral fat mass or ectopic lipid deposition in the liver and skeletal muscle either by gestation or by treatment group. There were no differences in fetal hepatic volume, hepatic lipid deposition or subcutaneous fat between the two treatment groups.

Myometrial biopsies

The number of myometrial biopsies obtained was too small and the distribution by treatment group following unblinding was too uneven to draw any reliable conclusions from this substudy.

Conclusions

Metformin given to obese pregnant women with normal glucose tolerance from 12–16 weeks' gestation until delivery has no significant effect on gestational age-, parity- and sex-adjusted birthweight centile. These results concur with those for lifestyle interventions in obese pregnant women, which have similarly little or no effect on birthweight centile. The metformin-associated reduction in IL-6 and CRP is of potential benefit but has to be set against the increase in diarrhoea and vomiting in women taking metformin.
The links between maternal obesity, offspring birthweight and detrimental effects on offspring health in adulthood remain of serious concern. Follow-up studies of the children born to the participants in this study are required to determine whether or not there are any longer-term benefits (or indeed harms) of maternal metformin in terms of their weight, fat mass and metabolism.

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Trial registration

This trial is registered as ISRCTN51279843.

Funding

This project was funded by the Efficacy and Mechanism Evaluation programme, a Medical Research Council and National Institute for Health Research partnership.

Chapter 1 Introduction and literature review

Rates of obesity, as defined by a body mass index (BMI) of > 30 kg/m^2, have risen alarmingly in recent decades. Around 20% of women booking for antenatal care in the UK are obese. The adverse effects of maternal obesity on pregnancy complications for both the mother and the fetus are well established[1–4] and there is mounting evidence of a detrimental effect on the longer-term health of offspring.[5–7] Increasingly, data suggest that maternal obesity may programme offspring later-life obesity, with high birthweight being a marker for increased risk. Our own recent work also suggests that offspring of obese pregnant women are at increased risk of premature death in adulthood.[8]

The mechanism by which maternal obesity causes excessive neonatal birthweight is not clearly understood but considerable evidence implicates insulin resistance and/or hyperglycaemia. Obese pregnant women are more insulin resistant and hyperglycaemic than their lean counterparts.[9] This enhances nutrient availability for the fetus with consequent excessive growth. There is a strong correlation between the degree of insulin resistance in late pregnancy and both birthweight and fat-free mass (FFM) at birth.[10] The Hyperglycaemia and Adverse Pregnancy Outcomes study[11] confirms that there is a linear relationship between hyperglycaemia and birthweight, even at glucose levels considered normal during pregnancy. Finally, treating hyperglycaemia in women with confirmed gestational diabetes mellitus (GDM) reduces the incidence of large-for-gestational-age (LGA) babies and other perinatal complications.[12]

The aim of this trial was to see whether or not giving the insulin-sensitising agent metformin to obese pregnant women from 12–16 weeks' gestation until delivery might reduce the future life risk of obesity and metabolic syndrome in the baby. We used birthweight centile as a surrogate marker for future life events as its predictive value has been shown in large epidemiological studies.[13]

Interventions in pregnancy to reduce excess birthweight in offspring of obese pregnant women

To date, all of the interventions that have been trialled in overweight or obese pregnant women to reduce the risk of excess birthweight in the offspring have involved modifications to diet or lifestyle, or a combination of both.

There have been several systematic reviews of studies evaluating such interventions in pregnancy but only two have been limited to overweight and obese women.[14,15] Three further randomised trials have been published since these reviews, the LIMIT trial (limiting weight gain in overweight and obese women during pregnancy to improve health outcomes),[16] the LiP (Lifestyle in Pregnancy) study[17] and UPBEAT (UK Pregnancies Better Eating and Activity Trial).[18]

The review by Dodd *et al.*[14] examined nine randomised controlled trials (RCTs) including 743 women. Seven trials compared a dietary intervention with standard antenatal care. Two of the trials evaluated the effect of an exercise intervention but outcomes did not include effect on infant birthweight in these studies. Only three trials reported outcome data for the primary outcome of LGA infants, with no significant difference between those who received the intervention and those who did not [366 women; risk ratio 2.20, 95% confidence interval (CI) 0.84 to 4.86]. Four trials examined effect on gestational weight gain and again there was no statistically significant difference between groups for this outcome (416 women; weighted mean difference –3.10 kg, 95% CI –8.32 to 2.13 kg). The overall conclusion of the review was that the evidence of benefit for this type of intervention in overweight or obese women is not clear. However, the authors noted that the quality of all of the included studies was poor to fair and that further high-quality, suitably powered randomised trials are urgently needed.

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The review by Oteng-Ntim *et al.*[15] included 13 randomised trials and six non-randomised trials. Again, the overall quality of the trials was deemed to be suboptimal, with five of the RCTs judged to be of medium quality and the rest of low quality. Six of the studies included LGA as an outcome, but there was no evidence that the interventions were associated with a lower prevalence of this outcome [1008 women; odds ratio (OR) 0.91, 95% CI 0.62 to 1.32]. Seven studies examined the effect on birthweight and, although there was a trend towards an effect of the intervention, this did not reach statistical significance (1133 women; mean difference –56.64 g, 95% CI –120.15 to 6.88 g). The authors reached a similar conclusion that further meta-analyses will be unlikely to refine the quality of the evidence and that large-scale suitably powered trials are required.

One such trial has since been published – the LIMIT trial.[16] This was a multicentre RCT of a diet, exercise and behavioural intervention compared with standard care for overweight or obese women (BMI of > 25 kg/m^2, median BMI of cohort 31.1 kg/m^2). The primary outcome was LGA infants (> 90th centile for gestation). The trial recruited to target a total of 2212 women and was adequately powered to detect a 30% reduction in LGA infants. There was no significant difference in the risk of infants born LGA in the lifestyle advice group compared with the standard care group (19% vs. 21%; adjusted risk ratio 0.90, 95% CI 0.77 to 1.07; $p = 0.24$).

The LiP study[17] was a smaller trial of 360 women, all of whom were obese (BMI of 30–45 kg/m^2, median BMI of 33 kg/m^2). The women were randomised to receive a lifestyle intervention that included dietetic advice, gym membership, physical training and personal coaching. The primary end point was a combination of five obstetric and neonatal outcomes: emergency caesarean section, pre-eclampsia, GDM, LGA and admission to the neonatal unit, with a score of 1 point for each outcome. There was no significant difference in combined scores between the groups (0.65 for the intervention group vs. 0.67 for the control group; $p = 0.39$). Birthweight was, in fact, significantly higher in the intervention group than in the control group (median 3742 g vs. 3596 g; $p = 0.039$). Gestational weight gain was significantly lower in the intervention group (7.0 kg vs. 8.6 kg; $p = 0.01$). However, as with many of the previous studies, the authors note that ultimately the study was underpowered, with power calculations being based on the expectation of a larger difference in gestational weight gain between groups than was actually found.

The UPBEAT[18] study similarly found no effect of a lifestyle intervention on the incidence of GDM or LGA infants.

At the time of initiation of the EMPOWaR study (Efficacy of Metformin in Pregnant Obese Women, a Randomised controlled trial), there were no RCTs of pharmacotherapy as an intervention for obese pregnant women. Given the evidence of a lack of effect from lifestyle interventions, pharmacotherapy is an important next step. Other than the work presented in this report, we are aware of two other ongoing studies of the effect of metformin as a pharmacological intervention in obese pregnant women [MOP (Metformin in Obese Pregnancy) – NCT01273584; and GRoW (metformin and dietary advice to improve insulin sensitivity and promote Gestational Restriction of Weight in pregnant women who are obese) – ACTRN12612001277831], one of which has now been published.[19]

Metformin in pregnancy

The use of metformin is endorsed by the National Institute for Health and Care Excellence for the treatment of GDM.[20] There are no placebo-controlled RCTs of the use of metformin in pregnancy, but several trials have compared metformin with alternative agents for the treatment of GDM. There have been several recent systematic reviews of these trials, including those by Balsells *et al.*[21] and Zhao *et al.*,[22] and a 'literature review' by Singh *et al.*[23] Additionally, two other randomised trials[24,25] have been published since these meta-analyses were performed.

The meta-analysis by Balsells *et al.*[21] compared metformin with insulin and with glibenclamide for the treatment of GDM. Fourteen primary outcomes were considered. Compared with insulin, metformin reduced maternal weight gain (mean difference −1.14 kg, 95% CI −2.22 to −0.06 kg), reduced gestational age at delivery (mean difference −0.16 weeks, 95% CI −0.30 to −0.02 weeks) and increased the rate of preterm births (risk ratio 1.50, 95% CI 1.04 to 2.16). Compared with glibenclamide, metformin reduced maternal weight gain (mean difference −2.06 kg, 95% CI −3.98 to −0.14 kg), was associated with lower birthweight (mean difference −209 g, 95% CI −314 to −104 g), reduced the risk of macrosomia (risk ratio 0.33, 95% CI 0.13 to 0.81) and reduced the risk of LGA newborns (risk ratio 0.44, 95% CI 0.21 to 0.92). Zhao *et al.*[22] demonstrated that, compared with insulin, metformin reduced the risk of pregnancy-induced hypertension (risk ratio 0.54, 95% CI 0.31 to 0.91), but there were no differences in effects on neonatal hypoglycaemia, LGA infants, respiratory distress syndrome, phototherapy or perinatal death.

The literature review[23] reported that the majority of studies found no difference in glycaemic control between metformin and insulin and suggested that, although there is a growing body of evidence to suggest a role for metformin in GDM management, much of this came from single-site small studies and that further studies are needed to inform guidelines.

In one of the RCTs not included in the systematic reviews described above,[25] and which recruited 159 women, metformin was demonstrated to be superior to glibenclamide because it was associated with a reduction in risk of 16.1% (95% CI 2.5% to 29.7%; $p = 0.02$) in the primary outcome, a composite of macrosomia, hypoglycaemia need for phototherapy, respiratory distress, stillbirth or neonatal death and birth trauma, largely because of a higher incidence of hypoglycaemia in the glibenclamide group.[25] In the RCT by Beyuo *et al.*[24] ($n = 104$), which compared metformin with placebo, with the addition of insulin if required to maintain glycaemic control, postprandial glucose levels were significantly lower in the metformin group.

There are few randomised trials of metformin compared with placebo in pregnant women without GDM. Both published studies were of women with polycystic ovary syndrome (PCOS),[26,27] with one being a pilot of the other. Although a significant difference in a composite of severe pregnancy and post-partum complications was seen in the smaller study comparing 850 mg of metformin twice daily with placebo ($n = 40$),[26] there were no significant differences in the outcomes of pre-eclampsia, preterm delivery and GDM in the larger study comparing 2000 mg of metformin daily with placebo ($n = 259$),[27] although women in the metformin group gained less weight.

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Chapter 2 Trial design and methods

Study design

This study was a double-blind, randomised, placebo-controlled trial in a population of obese pregnant women to examine the effect of metformin on sex- and age-adjusted birthweight centile of the baby. There were embedded substudies to explore the mechanism of action of metformin. In addition, a qualitative study was carried out to explore reasons for non-participation or non-retention of participants in the trial. A description of the trial protocol and a summary of the clinical trial results have already been published.[28,29]

Ethics approval and research governance

A summary of the protocol changes is provided in *Table 1*.

Ethics approval was obtained from Scotland A Research Ethics Committee (reference number 10/MRE00/12). The study was conducted in accordance with the principles of Good Clinical Practice.[30]

A Data Monitoring Committee oversaw the study. The trial was registered as ISRCTN51279843 (EMPOWaR).

Objectives

Primary objective

The primary objective was to determine the efficacy of metformin (up to 2500 mg daily) given to obese pregnant women from 12–16 weeks' gestation until delivery in reducing gestational age-, parity- and sex-adjusted birthweight centile of the baby.

Secondary objectives

- To determine the pattern of association between insulin resistance and adverse pregnancy outcomes including the incidence of pregnancy-induced hypertension, pre-eclampsia, caesarean section and post-partum haemorrhage, maternal weight gain during pregnancy and the incidence of the admission to the neonatal unit.
- To determine the effect of metformin on maternal body composition.
- To determine the effect of metformin on neonatal body composition.
- To determine the effect of metformin on maternal inflammatory and metabolic variables (measured at 28 and 36 weeks' gestation) and neonatal inflammatory variables (measured in cord blood at birth).
- To confirm that metformin does not increase the rate of babies with a low birthweight centile.
- To determine the efficacy (as opposed to the effectiveness) of metformin when analysis is restricted to those with pharmacological circulating levels of the drug.

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TABLE 1 Summary of protocol changes

Protocol version	Date	Summary of changes
1	6 January 2010	Initial protocol
1	4 March 2010	Additional information provided to Medicines and Healthcare products Regulatory Agency after initial non-acceptance
2	20 September 2010	Protocol modified to version 2
		Expanded details about the substudies
		Patient information leaflet and consent forms amended to version 3
		Addition of new site and principal investigator: Sheffield, Dr H Lashen
		Additional documents: treatment diary version 1, 16 June 2010; participant contact information sheet version 1, 13 September 2010; GP letter version 1, 20 September 2010
3	13 April 2011	Principal investigator contact address and site changed for Professor S Quenby
		Additional site and principal investigator: Nottingham, Dr Bugg
		Patient information leaflet and consent forms amended to version 4; all references to obesity removed
		Table of assessments errors corrected
		1-hour sampling time point in glucose tolerance test removed
		Paragraph 6.1 additional text added: 'where a letter inviting women to participate may be issued'
		GP letter, advert for newspaper, advert for waiting rooms (poster text) and slip for patient notes (invitation letter) updated to version 2
3	19 July 2011	Additional site and principal investigator: Bradford, Professor Tufnell
4	30 September 2011	Reference range for alanine aminotransferase changed
		Clarification of exclusion criteria for GDM
		Names of recruiting hospitals deleted from general protocol
		Reference to Matsuda index deleted; HOMA-IR to be used
4	13 February 2012	Patient advertising leaflet
		Addition of eight new sites
5	1 September 2013	Closure of site
		Revision of protocol for clarifications and addition of new substudy
		Revision of patient information leaflet and consent forms to version 5 and advertising leaflet to version 2
6	30 September 2013	Paragraphs 6.4 amendment and additional documents created for qualitative interviews
7	10 March 2014	Paragraphs 6.4 and 9.11 updated to include payment for substudy participants and inclusion of lean women as control subjects for vascular function substudy
8	24 September 2014	Updated protocol to clarify primary and secondary outcomes to agree with statistical analysis plan. Specifically, maternal insulin resistance at 36 weeks' gestation was originally a coprimary outcome, but was relegated to a secondary outcome when a substantial proportion of participants did not provide a blood sample at 36 weeks
		Removal of substudies to which no subjects were recruited

GP, general practitioner; HOMA-IR, homeostatic model assessment – insulin resistance.

Substudies

A series of nested substudies was also performed with the following objectives:

- to determine the effect of metformin on maternal cortisol levels in obese pregnant women
- to determine the effect of metformin on hepatic and peripheral insulin sensitivity at 36 weeks' gestation in obese pregnant women
- to determine the effect of metformin on endothelium-dependent flow-mediated dilatation (FMD) in obese pregnant women
- to determine the effect of metformin on maternal subcutaneous and visceral adipose tissue deposition and hepatic and skeletal muscle ectopic fat deposition during pregnancy
- to determine the effect of metformin on fetal liver volume and subcutaneous fat deposition
- to determine the effect of metformin on myometrial contractility and myometrial glycogen storage in obese pregnant women
- to determine the effect of metformin on placental glucocorticoid receptor and 11β-hydroxysteroid dehydrogenase (HSD) type 1 and 2 messenger ribonucleic acid (mRNA) levels.

Participants

The study sought to recruit obese pregnant women who met the following eligibility criteria.

Screening phase inclusion criteria

- Caucasian obese (BMI of ≥ 30 kg/m^2) pregnant women between 12^{+0} and 16^{+0} weeks' (+days) gestation.
- Aged ≥ 16 years.
- Signed informed consent form.

Screening phase exclusion criteria

- Non-Caucasian.
- BMI of < 30 kg/m^2.
- Gestation > 16 weeks.
- Pre-existing diabetes mellitus.
- GDM in a previous pregnancy.
- Systemic disease at the time of trial entry, with the disease either requiring regular medication or having required treatment with systemic steroids in the past 3 months.
- Previous delivery of a baby < 3rd centile by weight.
- Previous pregnancy complicated by pre-eclampsia prompting delivery before 32 weeks' gestation.
- Known sensitivity to metformin hydrochloride or any of the known excipients.
- Acute condition at the time of trial entry with the potential to alter renal function, such as dehydration sufficient to require intravenous infusion, severe infection, shock and intravascular administration of contrast agents.
- Acute or chronic diseases that may cause tissue hypoxia such as cardiac or respiratory failure, recent myocardial infarction, hepatic insufficiency, acute alcohol intoxication and alcoholism.
- Lactation.
- Multiple pregnancy.

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Randomisation exclusion criteria following screening

- GDM in index pregnancy [diagnosed with 75-g oral glucose tolerance test using World Health Organization (WHO) diagnostic criteria of fasting glucose ≥ 7.0 mmol/l, 2-hour glucose ≥ 7.8 mmol/l[31]]. Participants were also excluded if glucose tolerance testing was diagnostic of GDM based on the criteria used in the recruiting centre [e.g. International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria[32]].
- Liver or renal dysfunction at the time of trial entry tested prior to randomisation (urea > 6.6 mmol/l, creatinine > 85 mmol/l, sodium > 145 mmol/l, potassium > 5.0 mmol/l, bilirubin > 16 µmol/l, alanine transferase > 60 IU/l) or with abnormal lactate levels (according to local laboratory reference range).

Ineligible and non-recruited participants

No further information was collected on women who were ineligible because of abnormalities in glucose tolerance or liver or renal function, other than the number of such women for trial metrics.

Telephone or face-to-face interviews were carried out to explore the reasons for eligible women declining to participate (see *Chapter 5*).

Recruitment procedure

Potentially eligible subjects (i.e. women with a BMI of ≥ 30 kg/m^2 who booked to have their antenatal care at any of the participating hospitals) were either approached directly by a member of the research team or given written information by their caregiver and their contact details passed to the research team. The recruitment period was 3 February 2011 to 16 January 2014.

Informed consent

Subjects were given at least 24 hours to consider participation. They were then asked to provide written informed consent.

Randomisation, concealment and blinding

Eligible participants were randomly assigned to active treatment with metformin or an identical-looking placebo. This was documented in patients' paper case record and/or computer file to demonstrate their participation in the trial.

Participants were randomised via a web portal connected to a central randomisation facility based at the trial data centre, the Edinburgh Clinical Trials Unit, University of Edinburgh. Baseline eligibility criteria were required to be entered into the database before randomisation. Participants were randomised in a 1 : 1 ratio of metformin to placebo (block size of two to four). Randomisation was stratified by treatment centre and a BMI of 30–39 kg/m^2 compared with a BMI of > 40 kg/m^2.

Treatment group allocation

Randomising participants to active or placebo tablets achieved concealment of allocation. Placebo tablets appeared to be identical to active treatment so that participants were masked to treatment allocation. The outcomes were measured by clinicians and investigators masked to treatment allocation. Masking was not broken until after data entry was complete, the validity of the data was checked, all queries were resolved, the patient populations agreed and the database locked. Any clinically indicated unmasking was recorded prospectively.

Intervention

Metformin tablets (or matched placebo) (500 mg) were administered from as soon as practicable after the point of randomisation (and certainly between 12 and 16 weeks' gestation) until delivery of the baby. The dose regimen was as follows: week 1, 500 mg once daily; week 2, 500 mg twice daily; week 3, 500 mg three times a day; week 4, 500 mg morning and lunchtime and 1000 mg in the evening; week 5, 1000 mg in the morning and evening and 500 mg at lunchtime. All doses were taken with food and dose escalation continued to either the maximum tolerable dose or 2500 mg, whichever was higher.

Dose changes

Local investigators or participants were allowed to alter the treatment regimen at their discretion as long as the maximum daily dose did not exceed 2500 mg. Changes to the treatment dose were recorded in the electronic case report form as soon as was practicable.

Other medications

Alcohol was prohibited because of the increased risk of lactic acidosis. Iodinated contrast agents may increase the risk of renal failure and, hence, if they were required treatment was discontinued for at least 48 hours from immediately prior to contrast administration until after renal function had been re-evaluated and found to be normal. Clinicians prescribing glucocorticoids, beta-2-adrenoreceptor agonists and angiotensin-converting enzyme inhibitors should have been aware that they might amplify or diminish the hypoglycaemic effect of metformin.

Data collection and management

To standardise data collection processes across trial sites, researchers were trained to use detailed standard operating procedures (SOPs) for each element of data collection. Data were entered into the trial database contemporaneously and researchers were also encouraged to keep paper records as reference source data. A number of cross-checks were programmed into the database to automatically raise data queries, for example blank fields and values outwith reference ranges. The data were also checked manually on completion of data collection but prior to unblinding for extreme outliers in an attempt to ensure that biologically implausible data were confirmed or corrected.

Study assessments

Study assessments occurred over nine visits (either face to face or by telephone) throughout pregnancy. These are detailed in the study protocol (see *Appendix 1*) and are summarised in *Table 2*.

Maternal anthropometric measurements (waist, hip, upper arm and mid-thigh circumference and bicep, tricep and subscapular skinfold thickness) were recorded at baseline, at 36 weeks' gestation and at 3 months post partum (see *Appendix 2*). Neonatal anthropometric measurements (head circumference, length and tricep and subscapular skinfold thickness) were recorded within 72 hours of birth and at 3 months of age (see *Appendix 3*). All staff making anthropometry measurements were trained by the central trial team. We initially held a study training event on maternal and baby anthropometry for research midwives from Liverpool, Edinburgh and Coventry, during which all staff in attendance, including the trial manager, were trained by the investigators with experience in this area (SF, AD and RR). Further central training events were held with additional training offered and completed during the site initiation visits. All staff trained by the central team were then authorised to train new staff locally. The procedures were also documented in working practice documents, a set of instructions detailing the correct procedures for each measurement required.

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TABLE 2 Summary of study visits

	Visit number								
Purpose	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Gestation	10–16 weeks	10–16 weeks	12–16 weeks	18–20 weeks	28 weeks	36 weeks	Term	Labour/delivery/ neonatal	3 months postnatally
Assessment	Screening	Consent	Randomisation	Study visit (could be by telephone)	Study visit	Study visit	Study visit (could be by telephone)	Study visit	Study visit
Review inclusion and exclusion criteria	✗								
Patient information leaflet	✗								
Consent form		✗							
Demographics		✗							
Medical history		✗							
Height and weight		✗							✗
Maternal anthropometry		✗				✗			✗
Bloods for liver function/renal function/full lipid profile/ C-reactive protein		✗				✗			
75-g oral glucose tolerance test (sampling at baseline and 2 hours)		✗			✗	✗			
Stored sample for inflammatory and metabolic indices		✗			✗	✗			
Randomisation			✗						
Study drug dispensed			✗		✗				
Unused study drug/packaging returned								✗	

Purpose	Visit number 1	2	3	4	5	6	7	8	9
Review serious adverse events				✗	✗	✗	✗	✗	
Complete side effects questionnaire on eCRF				✗	✗	✗	✗	✗	
Review and record pregnancy complications				✗	✗	✗	✗	✗	
Saliva samples for cortisol measurements			✗		✗	✗			
BOD POD® measurements[a]		✗ (or visit 3)	✗ (or visit 2)			✗			✗
Hyperinsulinaemic–euglycaemic clamp						✗			
FMD			✗			✗			
Magnetic resonance scan					✗	✗			
Labour/delivery information including birthweight, mode of delivery, estimated blood loss								✗	
Cord blood and placenta biopsy								✗	
Myometrium biopsy (if delivered by caesarean section)								✗	
Adipose tissue biopsy								✗	
Baby's weight and anthropometry								✗	✗
PEA POD® measurements[a]								✗	✗

eCEF, electronic case report form.
a See www.lifemeasurement.com (accessed 21 June 2016).

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Glucose tolerance testing and fasting maternal blood samples were obtained at baseline and 28 and 36 weeks' gestation to determine the effect of metformin on glucose and insulin resistance. Glucose, C-reactive protein (CRP), liver function tests, urea and electrolytes and lipid indices were all analysed in the recruiting NHS hospital laboratory. These results were available to the clinical team immediately. Other serum and plasma samples were stored for later analysis of inflammatory and metabolic indices. These were insulin, interleukin (IL) 6, leptin, the plasminogen activator inhibitor-1 (PAI-1) : PAI-2 ratio, cortisol and non-esterified fatty acids (NEFAs). Umbilical cord blood was taken at the time of delivery for measurement of glucose and CRP and stored for future measurement of insulin, NEFAs, IL-6, leptin and cortisol.

All blood samples were collected, stored and transferred in accordance with the SOPs (see *Appendix 4*). The 75-g oral glucose tolerance test was performed in accordance with the SOPs (see *Appendix 4*). Urea and electrolytes, liver function tests, glucose, CRP, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and cholesterol were analysed by the recruiting NHS hospital laboratory.

Other analytical methods

Insulin

Insulin was measured using a standard sandwich enzyme-linked immunosorbent assay (ELISA) kit from Demeditec Diagnostics (Kiel, Germany). The limit of detection was 1.76 IU/l, with a mean intra-assay coefficient of variation (CV) of 2.2% and a mean inter-assay CV of 4.5%.

Interleukin 6

Interleukin 6 was measured using a high-sensitivity Quantikine® sandwich ELISA from R&D Systems (Abingdon, UK). The limit of detection was 0.039 pg/ml, with a mean intra-assay CV of 7.4% and a mean inter-assay CV of 7.8%.

Leptin

Leptin was measured using a standard sandwich ELISA kit from Alpco® (Salem, NH, USA). The limit of detection was 0.50 ng/ml, with a mean intra-assay CV of 4.6% and a mean inter-assay CV of 6.1%.

Plasminogen activator inhibitor 1

Plasminogen activator inhibitor 1 was measured using a sandwich ELISA kit from Cloud-Clone Corp. (Houston, TX, USA). The limit of detection was 0.063 ng/ml, with a mean intra-assay CV of < 10% and a mean inter-assay CV of < 12%.

Plasminogen activator inhibitor 2

Plasminogen activator inhibitor 2 was measured using a sandwich ELISA kit from Cloud-Clone Corp. The limit of detection was 0.61 ng/ml, with a mean intra-assay CV of < 10% and a mean inter-assay CV of < 12%.

Cortisol

Cortisol was measured using a standard ELISA kit from Demeditec Diagnostics. The limit of detection was 2.5 ng/ml, with a mean intra-assay CV of 5.6% and a mean inter-assay CV of 6.9%.

Non-esterified fatty acids

Non-esterified fatty acids were measured using an enzymatic colorimetric method assay kit from Wako Chemicals (Neuss, Germany). The assay range was 0.01–4.00 mEq/l. The mean intra-assay CV was not more than 1.5%.

Outcomes

Primary outcome

The primary outcome was z-score corresponding to the gestational age-, parity- and sex-adjusted birthweight centile of the baby.

Secondary outcomes

- Maternal insulin resistance at 36 weeks' gestation, which will be correlated with adverse pregnancy outcomes.
- Maternal anthropometry and body composition at 16 and 36 weeks' gestation and 3 months post-partum.
- Baby anthropometry and body composition at birth and 3 months of age.
- Maternal inflammatory markers and lipid and fatty acid indices prior to commencing treatment and again at 28 and 36 weeks' gestation, including CRP, IL-6, leptin, lipid profile, NEFAs, polyunsaturated fatty acids and PAI-1 : PAI-2 ratio.
- Neonatal CRP, glucose, insulin and other inflammatory and metabolic indices as previously described (measured in cord blood at birth).
- Incidence of low birthweight centile.
- Liquid chromatography-mass spectrometry measurement of metformin in maternal plasma to determine adherence.

Secondary outcomes from nested substudies

- Maternal salivary cortisol levels at baseline and 28 and 36 weeks' gestation.
- Hepatic and peripheral insulin sensitivity at 36 weeks' gestation as measured by the hyperinsulinaemic–euglycaemic clamp technique.
- Maternal brachial artery endothelium FMD measured at 16 and 36 weeks' gestation.
- Maternal subcutaneous and visceral adipose tissue deposition and hepatic and skeletal muscle ectopic fat deposition assessed using magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS).
- Fetal liver volume and fetal subcutaneous fat deposition assessed using MRI.
- In vivo measurements of myometrial contractility on myometrial biopsies obtained at the time of caesarean section.
- Placental glucocorticoid receptor and 11β-HSD1 and 11β-HSD2 mRNA levels.

Side effects and adverse events reporting

Participants were instructed to contact their investigator at any time after consenting to randomisation if any symptoms developed. In the case of any events, investigators initiated the appropriate treatment according to their medical judgement. Participants with adverse events present at their last visit were followed up until resolution of the event. All adverse events and serious adverse events (SAEs) that occurred after randomisation were recorded in detail in the participants' medical notes. SAEs occurring in the mother or baby from the time that a participant was randomised until 30 days after stopping taking the study treatment or 28 days after delivery (whichever was later) were reported to the cosponsors using the trial documentation (see *Appendix 5*). The standard definition of a SAE was used.[30] For the purposes of this study the following events were not considered SAEs: miscarriage; preterm labour; preterm, prelabour spontaneous rupture of membranes; preterm delivery in the maternal interest; preterm delivery in the fetal interest; hospitalisation for pregnancy-induced hypertension; hospitalisation for maternal discomfort; hospitalisation for rest; hospitalisation for observation or monitoring for which the woman was admitted for a period of < 12 hours; delivery complications such as caesarean section or post-partum haemorrhage; or admission of the baby to the neonatal unit for a period of up to 14 days.

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Sample size

We calculated that a sample size of 143 participants in each group would have 80% power to detect a difference in mean birthweight centile of 0.33 standard deviations (SDs) (equivalent to the difference between a placebo mean of 4000 g and a metformin mean of 3800 g) at the 5% significance level (two-sided) using a two-group *t*-test. We initially aimed to randomise 400 participants and anticipated high adherence and participant retention. We increased our sample size to 450 participants when it became apparent that adherence and retention were lower than anticipated.

Statistical analysis

Both intention-to-treat (ITT) analysis and per-protocol analysis are reported. ITT analysis uses data from all randomised participants by allocated treatment. Per-protocol analysis compares outcomes among only those who were compliant with treatment. Adherence was determined prior to review of the data and/or unblinding as follows: the number of weeks from randomisation to delivery was calculated for each participant and those participants reporting (using their study diary) that they took at least one tablet on at least 4 days per week for at least half of those weeks were deemed to have been compliant.

We performed exploratory analysis of secondary outcomes. No formal adjustment was made to any *p*-values to allow for the large numbers of secondary end points analysed and so the *p*-values for the secondary analyses should be interpreted conservatively. Post hoc analysis of safety outcomes of all reported SAEs and the combined outcomes of stillbirth, neonatal death, termination of pregnancy and miscarriage was also performed.

Birthweight centiles and z-scores of birthweight centiles (live births only) were derived for each patient after adjustment for sex, gestational age and parity (nulliparous vs. multiparous).[33] Z-scores were compared between the metformin group and the placebo group using a linear regression model, adjusted for treatment centre and BMI band (30–39 kg/m^2 vs. $\geq$ 40 kg/m^2) to obtain the adjusted mean difference (with 95% CI). This method was also used for other continuous outcomes including glucose, insulin and homeostatic model assessment – insulin resistance (HOMA-IR) measurement. When necessary, log transformations were performed to achieve a normal distribution of data prior to statistical testing. For umbilical cord blood CRP, Kruskal–Wallis one-way analysis of variance (ANOVA) was used, as this variable could not be transformed into a normal distribution. Unadjusted logistic regression for binary outcomes and Fisher's exact test were used when event counts were small. Relevant denominators were either all those randomised for whom information was available or those having a live birth for whom information was available.

A statistical analysis plan was finalised and 'signed off' before data lock and unblinding (see *Appendix 6*).

Analysis of the clinical main study outcome data was performed using the statistical programme SAS (version 9.3; SAS Institute Inc., Cary, NC, USA). Analysis of the substudy data was performed using the statistical programmes SAS (version 9.3) and Prism (version 6.0; GraphPad, La Jolla, CA, USA).

Chapter 3 Trial results

Recruitment

In total, 4867 women were approached to participate in the trial. Of these, 4418 were excluded for the following reasons: 2872 declined to participate, 730 did not meet the eligibility criteria, 752 were subsequently uncontactable, 56 were excluded for a variety of other reasons (e.g. they did not speak sufficient English or they were unable to attend extra hospital appointments) and eight did not attend the subsequent screening appointment. The majority of people initially approached to participate in the trial declined to do so. We were unable to formally quantify the reasons for this but anecdotally the most common reasons were a concern that the medication might be harmful to the baby and a lack of appreciation of the adverse effects of obesity on pregnancy outcomes.

Flow of participants through the trial

Figure 1 shows the flow of participants through the trial.

Baseline comparability

There were no differences between the two groups in terms of demographic or anthropometric characteristics at baseline (*Table 3*). Numbers recruited by each recruiting centre are shown in *Table 4*.

Losses to follow-up

Of the 449 women who were randomised, two withdrew and did not receive their treatment allocation. After the allocated treatment was issued, a further three withdrew from the study (including withdrawing their consent for analysis of the data) and one woman was lost to follow-up (see *Figure 1*). No participant was considered a protocol violator and no participants were unblinded to the study team before ascertainment of outcomes.

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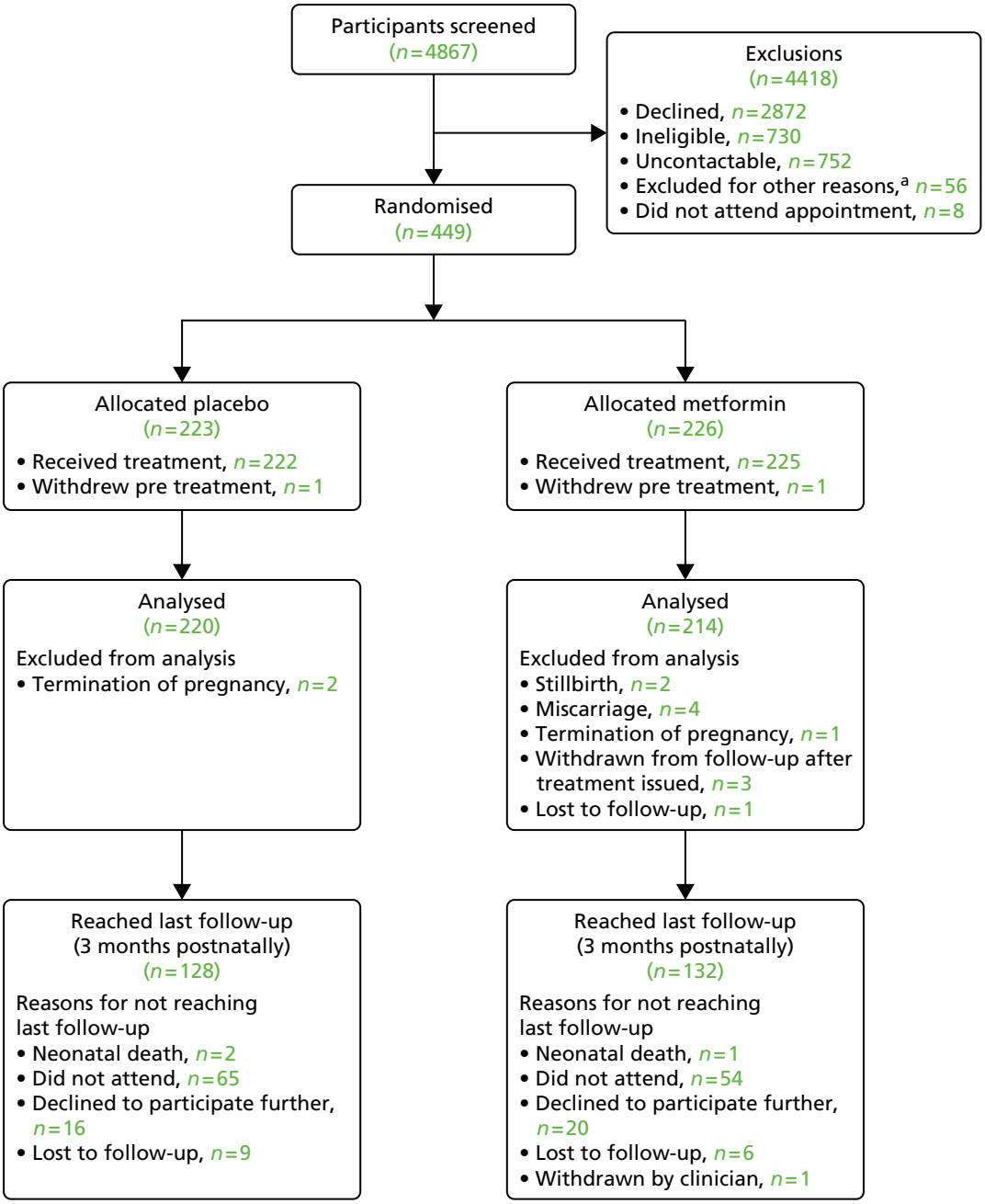


FIGURE 1 Flow of participants through the trial. a, Other reasons for non-recruitment: change in eligibility from screening of notes to recruitment visit [unable to arrange recruitment visit prior to 16 weeks ($n=26$), recruitment stopped prior to screening appointment ($n=14$), miscarriage ($n=2$), moved out of area ($n=1$)], unable to provide informed consent because of lack of spoken English-language ability ($n=5$), own doctor or midwife advised against participation ($n=4$) and duplicate note screening number issued in error ($n=4$).

TABLE 3 Baseline characteristics

Characteristics	ITT analysis[a]		Per-protocol analysis[a]	
	Placebo ($n = 223$)	Metformin ($n = 226$)	Placebo ($n = 118$)	Metformin ($n = 109$)
Demographics and lifestyle (participant)				
Age (years), mean (SD)	28.9 (5.1)	28.7 (5.8)	29.6 (5.0)	29.6 (5.6)
Current smoking, *n* (%)	31 (13.9)	40 (17.7)	13 (11.0)	13 (11.9)
Current alcohol use, *n* (%)	9 (4.0)	3 (1.3)	6 (5.1)	0 (0)
Illicit drug use, *n* (%)	1 (0.4)	0 (0)	0 (0)	0 (0)
Highest educational qualifications, *n* (%)				
Up to 16 years	79 (35.4)	75 (33.2)	37 (31.4)	26 (23.9)
> 16 years	144 (64.6)	151 (66.8)	81 (68.6)	83 (76.1)
At least one previous pregnancy of ≥ 12 weeks' gestation, *n* (%)	161 [220] (73.2)	147 (65.0)	87 (73.7)	68 (62.4)
Systolic blood pressure (mmHg), mean (SD)	119.4 (10.4)	117.6 (10.8)	119.3 (11.2)	117.1 (11.3)
Diastolic blood pressure (mmHg), mean (SD)	68.9 (7.3)	68.0 (7.8)	69.0 (7.7)	68.5 (7.9)
Gestation at recruitment (days), mean (SD)	98.9 (8.7)	99.1 (8.1)	98.9 (9.0)	100.0 (7.9)
Putative father, mean (SD)				
Height (cm)	178.5 (8.3)	177.1 (13.7)	178.5 (7.8)	177.9 (13.2)
Weight (kg)	92.3 (22.5)	93.5 (25.8)	92.1 (21.9)	94.6 (27.7)
Ethnicity, *n* (%)				
Caucasian	214 (96.0)	210 (93.8)	114 (96.6)	101 (92.7)
Mixed	4 (1.8)	4 (1.8)	1 (0.8)	2 (1.8)
Asian	0 (0)	3 (1.3)	0 (0)	2 (1.8)
Black	4 (1.8)	6 (2.7)	2 (1.7)	3 (2.8)
Chinese	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (0.4)	1 (0.4)	1 (0.8)	1 (0.9)

continued

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TABLE 3 Baseline characteristics (*continued*)

Characteristics	ITT analysis[a]		Per-protocol analysis[a]	
	Placebo ($n = 223$)	Metformin ($n = 226$)	Placebo ($n = 118$)	Metformin ($n = 109$)
Medical history (participant), *n* (%)				
Pre-eclampsia or pregnancy-induced hypertension	7 (3.1)	10 (4.4)	3 (2.5)	6 (5.5)
Pre-pregnancy hypertension requiring treatment	2 (0.9)	1 (0.4)	1 (0.8)	1 (0.9)
PCOS	21 (9.4)	28 (12.4)	14 (11.9)	16 (14.7)
Depression requiring treatment	71 (31.8)	48 (21.2)	33 (28.0)	24 (22.0)
Anxiety requiring treatment	20 (9.0)	15 (6.6)	7 (5.9)	7 (6.4)
Family history (participant), *n* (%)				
Cardiovascular disease	69 (30.9)	71 (31.4)	41 (34.7)	31 (28.4)
Pre-eclampsia	22 (9.9)	19 (8.4)	8 (6.8)	4 (3.7)
Diabetes mellitus	101 (45.3)	99 (43.8)	54 (45.8)	47 (43.1)
Other	96 (43.0)	109 (48.2)	58 (49.2)	57 (52.3)
Participant anthropometry, mean (SD)				
Height (cm)	165.1 (5.9)	165.5 (5.9)	166.1 (6.0)	165.8 (5.7)
Weight (kg)	102.9 (17)	103.6 (15.5)	103.7 (17.0)	104.0 (15.2)
BMI calculated (kg/m^2)	37.7 (5.6)	37.8 (5.0)	37.5 (5.5)	37.8 (4.7)
Waist (cm)	108.7 [222] (13.5)	110.1 [225] (11.9)	108.3 (12.6)	108.6 (11.2)
Hip (cm)	126.4 [222] (12.1)	127.4 [225] (11.8)	126.8 (11.6)	127.5 (12.2)
Mid-arm (cm)	36.3 [220] (5.0)	36.7 [221] (4.7)	36.6 (4.7)	37.1 (4.4)
Mid-thigh (cm)	64.1 [219] (7.7)	64.2 [222] (6.9)	64.2 (7.3)	65.3 (7.0)
Tricep skinfold (mm)	31.2 [222] (9.7)	31.9 [222] (10.8)	33.3 (9.4)	32.6 (9.7)
Bicep skinfold (mm)	25.7 [222] (10.0)	27.4 [222] (10.9)	27.4 (10.1)	27.8 (10.7)
Subscapular skinfold (mm)	32.0 [222] (12.2)	32.6 [220] (11.8)	35.3 (11.0)	34.8 (11.7)
% fat[b]	46.8 [48] (5.6)	48.2 [53] (5.2)	46.2 (5.2)	48.6 (5.0)

Characteristics	ITT analysis[a]		Per-protocol analysis[a]	
	Placebo ($n = 223$)	Metformin ($n = 226$)	Placebo ($n = 118$)	Metformin ($n = 109$)
Baseline bloods (recruitment visit), mean (SD)				
Gestation of sampling (days)	101.1 (8.1)	100.8 (7.4)	98.9 (9.0)	100.0 (7.9)
Fasting glucose (mmol/l)	4.39 (0.34)	4.41 (0.40)	4.42 (0.36)	4.41 (0.37)
2-hour glucose (mmol/l)[c]	5.50 (1.09)	5.20 (1.08)	5.54 (1.18)	5.17 (1.10)
Fasting insulin (μIU/ml)	22.08 [189] (10.20)	21.95 [188] (12.26)	22.96 [101] (10.46)	21.92 [92] (8.99)
HOMA-IR score[d]	4.36 [189] (2.16)	4.36 [188] (2.76)	4.59 [101] (2.32)	4.34 [92] (1.82)
CRP (mg/l)	11.1 (7.4)	10.7 (6.9)	11.4 (7.9)	10.0 (6.3)
Cholesterol (mmol/l)	4.87 (1.15)	4.88 (1.09)	4.86 [117] (1.16)	4.82 [108] (1.13)
HDL (mmol/l)	1.67 (0.39)	1.64 (0.38)	1.67 [117] (0.38)	1.64 [108] (0.39)
LDL (mmol/l)	2.91 (0.78)	2.89 (0.86)	2.98 [106] (0.75)	2.90 [101] (0.90)
Triglycerides (mmol/l)	1.51 (0.53)	1.43 (0.56)	1.51 [117] (0.54)	1.45 [108] (0.58)

a *n* is shown in square brackets for individual characteristics when it is different from the total number randomised.
b Measured only in Edinburgh participants.
c After a 75-g oral glucose challenge.
d Fasting glucose (in mmol/l) × insulin (in μIU/ml)/22.5.

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TABLE 4 Recruiting centres

Recruiting centre	Placebo ($n = 223$), n (%)	Metformin ($n = 226$), n (%)	Overall ($n = 449$), n (%)
Royal Infirmary of Edinburgh	60 (26.9)	59 (26.1)	119 (26.5)
University Hospital Coventry and Warwickshire	49 (22.0)	49 (21.7)	98 (21.8)
Liverpool Women's Hospital	38 (17.0)	39 (17.3)	77 (17.1)
Sheffield Teaching Hospital	24 (10.8)	24 (10.6)	48 (10.7)
Nottingham City Hospital	7 (3.1)	6 (2.7)	13 (2.9)
Nottingham Queen's Medical Centre	8 (3.6)	6 (2.7)	14 (3.1)
Bradford Royal Infirmary	4 (1.8)	4 (1.8)	8 (1.8)
Whiston Hospital, St Helens and Knowsley Hospitals	1 (0.4)	3 (1.3)	4 (0.9)
Chelsea and Westminster Hospital	0	1 (0.4)	1 (0.2)
Royal Preston Hospital	18 (8.1)	18 (8.0)	36 (8.0)
Arrowe Park Hospital, Wirral	3 (1.3)	4 (1.8)	7 (1.6)
Chesterfield Royal Hospital	11 (4.9)	12 (5.3)	23 (5.1)
Royal Blackburn Hospital	0	1 (0.4)	1 (0.2)

Two centres did not recruit any participants and so are not listed.

Adherence to the intervention

From participant diary returns and analysis using predefined criteria, 118 out of 177 (67%) in the placebo group and 109 out of 167 (65%) in the metformin group were deemed 'adherent'. If those who did not return their diary were assumed not to be adherent, calculated adherence would fall to 53% and 48%, respectively. Subsequent analysis of metformin levels showed that detectable levels of metformin were present in the blood of 80 out of 131 (61%) women in the metformin group who gave a blood sample at 36 weeks' gestation. To explore dosage, we determined the proportion of drug-taking days when 2500 mg or 2000 mg of study drug was taken. Over the entire study, there were 35,686 days when diary data indicated consumption of at least one tablet of study drug. In the placebo group, for 56% of those days the maximum dose of 2500 mg was taken and for 68% of those days a dose of $\geq$ 2000 mg was taken. The corresponding figures for the metformin group were 38% and 62%.

Primary outcome

Mean (SD) birthweight at delivery was 3463 g (660 g) in the placebo group and 3462 g (548 g) in the metformin group. The primary outcome of z-score of birthweight centile for babies live-born at $\geq$ 24 weeks' gestation, adjusted for gestation at delivery, parity and sex, was similar in the placebo and metformin groups for both the ITT analysis (adjusted mean difference –0.029, 95% CI –0.271 to 0.158; $p = 0.7597$) and the per-protocol analysis (adjusted mean difference 0.068, 95% CI –0.188 to 0.324; $p = 0.6001$) (*Table 5*). The distribution of the primary outcome in the two treatment groups is shown in *Figure 2*.

TABLE 5 Primary outcome and birth outcome data

Outcome	ITT					Per protocol				
	Placebo	Metformin	Adjusted mean difference	95% CI	*p*-value	Placebo	Metformin	Adjusted mean difference	95% CI	*p*-value
Primary outcome [*N*], mean (SD)										
z-score of birthweight centile[a]	0.2680 [220] (1.0055)	0.2464 [214] (1.0179)	–0.029	–0.217 to 0.158	0.7597	0.3130 [117] (0.9781)	0.3604 [108] (1.0580)	0.068	–0.188 to 0.324	0.6001
Birth outcome (all births) [*N*], *n* (%)										
Live births at ≥ 24 weeks' gestation	220 [222] (99.1)	214 [221] (96.8)				117 [118] (99.2)	108 [108] (100)			
Stillbirths at ≥ 24 weeks' gestation, miscarriage or termination of pregnancy	2[b] [222] (0.9)	7[c] [221] (3.2)	3.597[d]	0.739 to 17.504	0.113	1 (0.8)	0 (0)	< 0.001[d]	< 0.001 to > 999.999	0.9604
Birth outcome (babies live-born at ≥ 24 weeks' gestation)										
Gestational age at delivery (days) [*N*], mean (SD)	275.9 [220] (15.9)	276.6 [214] (11.7)				277.6 [117] (12.7)	276.6 [108] (11.5)			
Male sex [*N*], *n* (%)	109 [220] (49.5)	109 [214] (50.9)				58 [118] (49.2)	54 [108] (50)			
Birthweight at delivery (g) [*N*], mean (SD)	3463 [220] (660)	3462 [214] (548)				3539.0 [117] (553.9)	3503.6 [108] (562.8)			
Birthweight centile [*N*], mean (SD)	57.3 [220] (27.9)	56.9 [214] (28.6)				58.527 [117] (27.7)	59.894 [108] (28.3)			

a Centile by gestational age, sex and parity for live births at ≥ 24 weeks' gestation.
b Two terminations of pregnancy, one for fetal abnormality (split hand and foot syndrome) and one following spontaneous rupture of the membranes at 18 weeks' gestation.
c Two stillbirths, one at 31 weeks' gestation of a baby with a known congenital cardiac anomaly and severe hydrops and one was an intrauterine death of a normally formed baby born at 38 weeks' gestation at < 3rd centile for birthweight; four miscarriages, one following a road traffic accident with the other three being spontaneous; and one termination of pregnancy following a diagnosis of trisomy 21. None of these women completed any diary entries or provided a blood sample for analysis of metformin.
d OR, post hoc analysis.

Note
Shading represents data not calculated.

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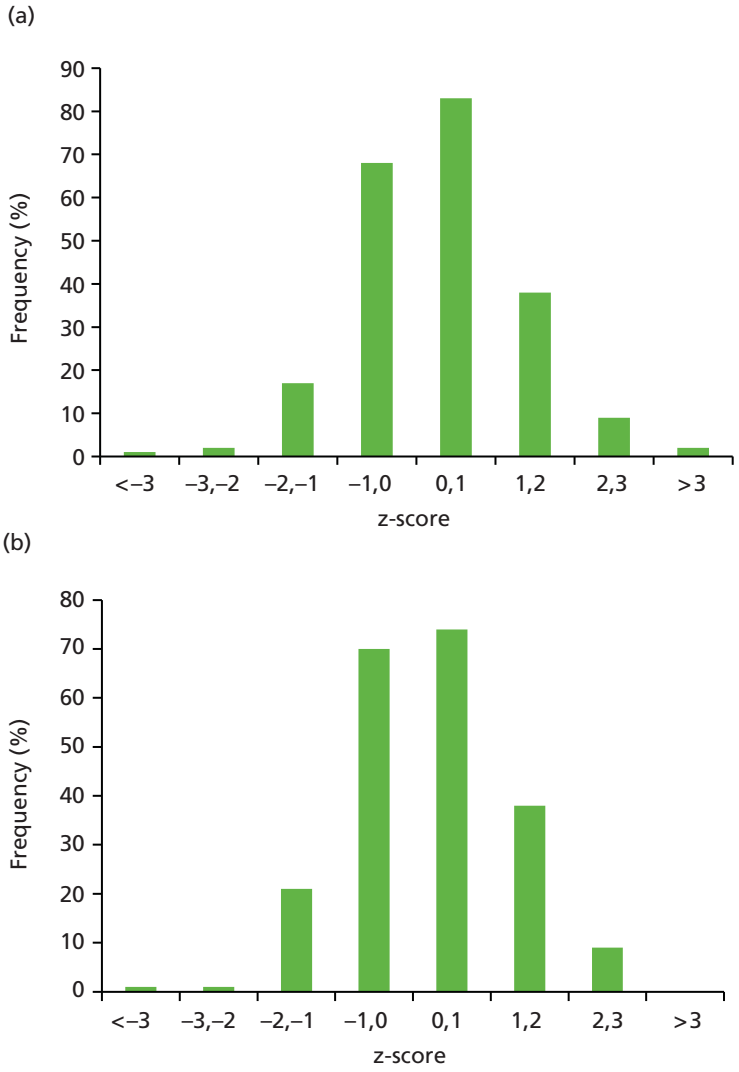


FIGURE 2 Distribution of the primary outcome (birthweight) in the (a) placebo and (b) metformin groups.

Secondary outcomes

Maternal outcomes

There was no evidence of a reduction in the main secondary outcome of HOMA-IR at 36 weeks' gestation (*Table 6*). Mean HOMA-IR in the placebo and metformin groups was 5.98 and 6.30 molar units, respectively (adjusted mean ratio 0.974, 95% CI 0.865 to 1.097). Similarly, there was no evidence of a statistically significant effect of metformin on fasting or 2-hour glucose (after a 75-g oral glucose challenge) or fasting insulin at 36 weeks' gestation (see *Table 6*). However, fasting glucose and the HOMA-IR score at 28 weeks' gestation were lower in the metformin group (adjusted mean difference/ratio –0.105 mmol/l, 95% CI –0.193 to –0.016 mmol/l; and 0.895 molar units, 95% CI 0.803 to 0.998 molar units, respectively) (data not shown).

Metformin had no effect on maternal weight gain during pregnancy (adjusted mean difference in weight gain –0.680 kg, 95% CI –1.863 to 0.503 kg) or maternal weight retention at 3 months post partum (*Table 7*). We subsequently performed an analysis of weight gain adjusted for baseline weight and again found no significant effect of metformin on weight gain (adjusted mean difference in weight gain –0.637 kg, 95% CI –1.819 to 0.544 kg). There were no differences in the other anthropometric measures of waist, hip, mid-arm and mid-thigh circumference or bicep, tricep and subscapular skinfold thickness (see *Table 7*).

TABLE 6 Secondary outcomes: biochemistry

	ITT							Per protocol						
	Placebo		Metformin					Placebo		Metformin				
Outcome	Mean (*n*)	SD	Mean (*n*)	SD	Adjusted mean difference/ratio	95% CI	*p*-value	Mean (*n*)	SD	Mean (*n*)	SD	Adjusted mean difference/ratio	95% CI	*p*-value
Maternal biochemistry at 36 weeks' gestation														
Fasting glucose (mmol/l)	4.42 (151)	0.48	4.35 (143)	0.45	–0.060	–0.163 to 0.043	0.250	4.43 (104)	0.51	4.34 (93)	0.45	–0.091	–0.221 to 0.040	0.1726
2-hour glucose (mmol/l)[a]	5.96 (148)	1.46	5.70 (142)	1.32	–0.251	–0.565 to 0.062	0.116	6.04 (103)	1.53	5.79 (92)	1.34	–0.248	–0.643 to 0.148	0.2179
Fasting insulin (μIU/ml)	30.09 (131)	13.12	32.79 (127)	24.55	1.005	0.901 to 1.120	0.934	31.89 (88)	13.40	32.59 (79)	26.07	0.939	0.819 to 1.075	0.3576
HOMA-IR score[b]	5.98 (131)	2.89	6.30 (123)	4.78	0.974	0.865 to 1.097	0.666	6.36 (88)	2.96	6.22 (77)	4.90	0.912	0.784 to 1.060	0.2290
CRP (mg/l)	9.20 (150)	7.10	7.47 (140)	4.62	0.860	0.743 to 0.996	0.043	8.91 (104)	6.39	7.48 (93)	4.58	0.901	0.760 to 1.070	0.2329
Cholesterol (mmol/l)	6.32 (144)	1.44	6.33 (139)	1.74	1.004	0.954 to 1.056	0.875	6.29 (100)	1.54	6.16 (91)	1.88	0.974	0.913 to 1.039	0.4230
HDL (mmol/l)	1.70 (145)	0.38	1.76 (138)	0.43	0.051	–0.040 to 0.142	0.273	1.71 (100)	0.37	1.76 (91)	0.38	0.055	–0.046 to 0.155	0.2866
LDL (mmol/l)	3.57 (126)	1.13	3.77 (118)	1.25	1.064	0.982 to 1.152	0.127	3.67 (89)	1.09	3.71 (80)	1.22	1.013	0.923 to 1.113	0.7793
Triglycerides (mmol/l)	2.79 (146)	0.84	2.76 (140)	0.88	0.993	0.926 to 1.064	0.833	2.79 (101)	0.90	2.84 (92)	0.96	1.031	0.942 to 1.127	0.5073
IL-6 (mmol/l)	3.86 (131)	4.10	2.93 (127)	1.37	0.847	0.754 to 0.952	0.006	3.66 (88)	3.73	2.77 (79)	1.26	0.858	0.745 to 0.988	0.0333
Leptin (ng/ml)	105.0 (131)	52.4	106.6 (127)	58.8	1.005	0.902 to 1.120	0.927	103.80 (88)	55.34	101.26 (79)	47.02	1.007	0.886 to 1.145	0.9152

continued

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TABLE 6 Secondary outcomes: biochemistry (*continued*)

	ITT							Per protocol						
	Placebo		Metformin					Placebo		Metformin				
Outcome	Mean (*n*)	SD	Mean (*n*)	SD	Adjusted mean difference/ratio	95% CI	*p*-value	Mean (*n*)	SD	Mean (*n*)	SD	Adjusted mean difference/ratio	95% CI	*p*-value
Serum cortisol (nmol/l)	821.7 (131)	232.9	867.0 (127)	225.5	1.062	0.999 to 1.128	0.052	806.48 (88)	225.00	888.39 (79)	250.73	1.092	1.010 to 1.181	0.0281
NEFA (mmol/l)	0.47 (131)	0.18	0.46 (127)	0.19	0.947	0.859 to 1.044	0.273	0.47 (88)	0.19	0.48 (79)	0.21	1.041	0.919 to 1.179	0.5249
PAI1/PAI2 ratio	3.20 (131)	2.61	2.97 (128)	2.79	0.913	0.771 to 1.081	0.291	3.40 (91)	2.65	3.31 (82)	3.09	0.895	0.721 to 1.113	0.3167
Cord blood biochemical outcomes														
Glucose (mmol/l)	3.89 (79)	1.24	4.06 (74)	1.08	1.067	0.974 to 1.170	0.164	3.94 (62)	1.25	4.02 (54)	1.05	1.062	0.955 to 1.181	0.2626
Insulin (µIU/ml)	10.95 (47)	7.49	11.41 (57)	8.80	1.060	0.767 to 1.463	0.722	11.14 (37)	7.48	12.04 (45)	9.21	1.137	0.805 to 1.607	0.4602
HOMA-IR score[b]	1.92 (38)	1.39	1.91 (41)	2.00	1.012	0.701 to 1.462	0.947	1.83 (32)	1.36	1.93 (30)	2.19	1.066	0.720 to 1.579	0.7436
CRP (mg/l)[c]	4.32 (78)	19.55	2.36 (73)	2.29			0.741	4.85 (62)	21.89	2.15 (53)	1.82			0.7987

a After a 75-g oral glucose challenge.
b Fasting glucose (in mmol/l) × insulin (µIU/ml)/22.5.
c Kruskal–Wallis non-parametric test used.

TABLE 7 Secondary outcomes: maternal and neonatal anthropometry

	ITT								Per protocol							
	36 weeks				3 months post-partum				36 weeks				3 months post-partum			
	Placebo		Metformin		Placebo		Metformin		Placebo		Metformin		Placebo		Metformin	
Outcome	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD
Maternal anthropometry																
Height (cm)	166.0 (153)	6.0	166.3 (142)	5.6	165.3 (125)	5.9	166.1 (127)	5.8	166.2 (105)	6.1	166.4 (94)	5.7	165.6 (89)	6.0	166.2 (89)	5.7
BMI (kg/m^2)	40.4 (153)	5.4	40.6 (141)	4.9	37.4 (124)	5.2	38.3 (124)	5.6	40.2 (105)	5.4	40.4 (93)	4.7	37.1 (89)	4.9	38.0 (87)	5.5
Waist (cm)	120.0 (155)	13.2	119.0 (142)	11.1	109.2 (124)	12.8	109.9 (125)	13.9	119 (106)	12.6	117.4 (93)	10.9	108.4 (88)	13.0	109.3 (89)	13.2
Hip (cm)	130.1 (155)	12.3	131.3 (142)	11.8	127.3 (124)	12.2	128.6 (125)	13.4	129.8 (106)	11.9	131.1 (93)	11.8	127.1 (88)	12.0	127.7 (89)	13.4
Mid-arm (cm)	36.5 (154)	4.9	36.5 (142)	4.4	37.1 (123)	4.7	37.4 (125)	4.4	36.4 (105)	4.7	36.4 (93)	4.4	37.2 (87)	4.6	37.0 (89)	4.2
Mid-thigh (cm)	65.3 (154)	7.4	65.2 (139)	6.8	64.3 (122)	6.7	65.8 (124)	6.8	64.8 (105)	7.2	65.7 (93)	6.6	64.7 (86)	6.3	65.7 (88)	6.7
Tricep skinfold (mm)	30.4 (155)	10.3	31.3 (143)	12.0	32.2 (123)	10.8	33.4 (125)	11.4	31.4 (106)	9.4	33.4 (94)	11.5	33.1 (87)	11.0	33.8 (89)	12.6
Bicep skinfold (mm)	26.0 (155)	10.5	26.9 (143)	11.6	27.2 (123)	12.1	29.7 (125)	15.1	26.7 (106)	10.3	28.4 (94)	12.2	27.5 (87)	12.5	29.5 (89)	16.5
Subscapular skinfold (mm)	32.7 (154)	13.5	34.5 (141)	13.9	33.2 (123)	13.1	35.9 (124)	13.2	34.9 (105)	13.1	36.3 (92)	12.6	35.1 (87)	13.3	36.4 (89)	12.8
Maternal % fat[a]	46.3 (31)	4.84	47.8 (30)	4.63	47.45 (29)	4.97	48.35 (30)	5.31	45.6 (22)	4.7	47.4 (29)	4.7	46.8 (21)	5.0	48.5 (27)	4.8
Weight gain during pregnancy (kg)	7.23 (156)	4.91	6.70 (143)	6.00	–0.13 (124)	6.22	0.07 (124)	9.82	7.40 (106)	4.6	6.85 (93)	6.1	0.05 (89)	6.1	0.83 (87)	11.0

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TABLE 7 Secondary outcomes: maternal and neonatal anthropometry (*continued*)

	ITT								Per protocol							
	Within 72 hours of birth				3 months of age				Within 72 hours of birth				3 months of age			
	Placebo		Metformin		Placebo		Metformin		Placebo		Metformin		Placebo		Metformin	
Outcome	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD	Mean (*n*)	SD
Neonatal anthropometry (live births only)																
Age at which measurements made (days)	1.04 (157)	2.44	0.97 (145)	2.44	99.59 (128)	13.12	97.72 (129)	14.01	1.34 (97)	3.0	1.12 (89)	2.6	99.95 (91)	11.9	96.84 (90)	13.9
Length (cm)[b]	51.2 (150)	4.0	50.7 (139)	3.3	62.13 (124)	4.4	61.69 (125)	6.33	51.4 (94)	3.0	51.1 (83)	3.3	62.41 (89)	3.9	61.51 (90)	7.2
Head circumference (cm)	34.7 (164)	4.2	34.8 (152)	3.6	41.30 (124)	2.87	41.02 (122)	4.42	35.32 (99)	1.8	34.88 (89)	4.5	41.08 (89)	2.0	41.11 (88)	5.1
Ponderal index [mass (g)/height (cm)^3][b]	2.6 (143)	0.41	2.67 (130)	0.50	2.58 (124)	0.82	2.52 (124)	1.00	2.64 (90)	0.42	2.63 (79)	0.46	2.48 (89)	0.6	2.59 (89)	1.05
Tricep skinfold thickness (mm)	14.3 (111)	20.6	16.4 (99)	27.9	22.05 (106)	10.40	24.61 (104)	11.00	16.26 (79)	22.0	17.29 (74)	30.1	23.98 (83)	35.6	25.67 (83)	36.0
Subscapular skinfold (mm)	13.5 (113)	20.4	15.7 (98)	28.0	17.00 (104)	23.95	23.11 (104)	31.33	14.84 (80)	21.1	15.88 (73)	29.5	17.80 (82)	25.1	24.70 (83)	33.1
Baby % fat[a]	12.1 (22)	5.7	12.9 (21)	4.5	25.88 (31)	6.13	23.19 (29)	5.91	13.45 (15)	5.8	12.77 (20)	4.6	25.80 (22)	5.9	23.33 (26)	5.7
Weight at this time (g)[b,c]	3707.76 (164)	2685.66	3455.18 (146)	545.08	6085.04 (128)	1276.59	5971.97 (132)	1724.20	3564.96 (97)	513.5	3492.74 (85)	578.5	6075.67 (90)	1362.0	6108.76 (91)	1664.0

a Measured only in Edinburgh participants.
b Outliers outside ±6 SDs were removed.
c Baby weight was recorded on two occasions – at birth by the delivery team (figure used for z-score calculations) and then at the time of taking the research measurements by the research team (this second figure is shown here and is used for calculation of the ponderal index).

Plasma IL-6 and CRP concentrations were both lower in the group treated with metformin at 36 weeks' gestation (adjusted mean ratio 0.847 mmol/l, 95% CI 0.754 to 0.952 mmol/l; and 0.860 mg/l, 95% CI 0.743 to 0.996 mg/l, respectively). Cholesterol, HDL, LDL, triglycerides, leptin, NEFA and PAI1/2 ratio at 36 weeks' gestation were similar in the two groups. There was a trend towards higher serum cortisol at 36 weeks' gestation in the metformin group on ITT analysis and this reached statistical significance in the per-protocol analysis (adjusted mean ratio 0.088, 95% CI 0.010 to 0.167; $p = 0.0281$) (see *Table 6*).

Metformin did not appear to prevent GDM. The proportion of women fulfilling either the IADPSG or the WHO criteria for GDM at any time in pregnancy was similar in the two groups. Post hoc analysis of the timing of diagnosis of GDM (IADPSG criteria) showed no statistically significant difference between the two groups: in the placebo group 26 women were diagnosed at 28 weeks' gestation and 10 at 36 weeks' gestation, whereas in the metformin group 11 women were diagnosed at 28 weeks' gestation and 15 at 36 weeks' gestation ($p = 0.0718$, Mantel–Haenszel chi-square, post hoc analysis); however, the trend was towards a later diagnosis in the metformin-treated group.

There were no differences in outcomes at other time points between the two groups, with the exception of fasting glucose and HOMA-IR score, as mentioned previously.

Further analysis of the data on a per-protocol basis resulted in similar findings with a few exceptions. For CRP at 36 weeks' gestation and vomiting, the direction of difference was maintained but statistical significance was lost. Two-hour glucose and fasting insulin at 28 weeks' gestation were lower in the metformin group (estimated mean difference –0.312 mmol/l, 95% CI –0.620 to –0.004 mmol/l; $p = 0.0471$; and 0.871 µIU/ml, 95% CI 0.778 to 0.976 µIU/ml; $p = 0.0173$, respectively). Serum cortisol at 36 weeks' gestation was higher in the metformin-treated group (estimated mean difference 0.088 nmol/l, 95% CI 0.010 to 0.167 nmol/l; $p = 0.0281$) (summarised in *Table 7*).

At 36 weeks' gestation there were no differences in serum B_{12} or folate levels between the two groups on ITT analysis (adjusted mean difference: B_{12} 0.952 ng/l, 95% CI 0.879 to 1.032 ng/l; $p = 0.2296$; folate 1.050 µg/l, 95% CI 0.885 to 1.247 µg/l; $p = 0.5737$). However, on per-protocol analysis, participants in the metformin group had a lower serum B_{12} concentration at 36 weeks' gestation (adjusted mean difference 0.890 ng/l, 95% CI –0.804 to 0.985 ng/l; $p = 0.0248$). There were no differences between the groups in the proportion of participants with a serum B_{12} or folate concentration < 5th centile (*Table 8*).

Neonatal outcomes

The proportion of live-born babies weighing > 90th centile was similar in the two groups [placebo 38/220 (17%), metformin 31/214 (14%)]. Importantly, we also did not see a difference in the proportion of babies weighing < 10th centile [placebo 11/220 (5%), metformin 14/214 (7%)]. There was no significant difference in neonatal ponderal index at birth between the two groups (adjusted mean ratio 1.032 g/cm^3, 95% CI 0.996 to 1.069 g/cm^3).

Neonatal cord blood glucose, insulin, HOMA-IR and CRP were similar in the two groups (see *Table 6*).

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TABLE 8 Secondary outcomes: serum B_{12} and folate

	ITT					Per protocol				
Outcome	Placebo	Metformin	Adjusted mean difference	95% CI	*p*-value	Placebo	Metformin	Adjusted mean difference	95% CI	*p*-value
Serum B_{12} (ng/l) [*n*], mean (SD)[a]										
Baseline	260.2 [132] (101.3)	266.3 [131] (92.4)				256.6 [90] (108.1)	259.4 [82] (71.6)			
36 weeks[b]	223.7 [130] (69.6)	215.0 [132] (73.2)	0.952	0.879 to 1.032	0.2296	226.1 [88] (75.4)	205.5 [83] (68.6)	0.890	0.804 to 0.985	0.0248
Proportion with serum B_{12} < 5th centile, *n* (%)										
Baseline	8 (6.1)	5 (3.8)				6 (6.7)	4 (4.9)			
36 weeks	6 (4.6)	7 (5.3)	1.157[c]	0.378 to 3.541	0.7979	5 (5.7)	6 (7.2)	1.294[c]	0.379 to 4.411	0.6809
Serum folate (µg/l) [*n*], mean (SD)[d]										
Baseline	13.84 [132] (4.6)	13.77 [131] (4.8)				13.93 [90] (4.6)	14.48 [82] (4.4)			
36 weeks[b]	8.29 [132] (5.6)	8.54 [132] (5.6)	1.050	0.885 to 1.247	0.5737	9.15 [90] (6.0)	9.46 [83] (5.7)	1.114	0.897 to 1.384	0.3263
Proportion with serum folate < 5th centile, *n* (%)										
Baseline	0 (0)	2 (1.5)				0 (0)	1 (1.2)			
36 weeks	10 (7.6)	11 (8.3)	1.109[c]	0.454 to 2.708	0.8201	7 (7.8)	5 (6.0)	0.760[c]	0.232 to 2.495	0.6510

a Reference range used 200–940 ng/l, 5th centile set at 117 ng/l.
b This parameter was log-transformed for statistical analysis and the results back transformed for this table.
c OR.
d Reference range used was 3.1–17.5 µg/l, 5th centile was set at 2.6 µg/l.

Note
Shading represents data not calculated.

Adverse events

Maternal symptoms of diarrhoea and vomiting were more common in the metformin group (OR 1.670, 95% CI 1.064 to 2.621; and 3.113, 95% CI 1.975 to 4.908 in the placebo and metformin groups, respectively).

The incidence of other adverse outcomes, including preterm birth and low birthweight, caesarean section and post-partum haemorrhage, was similar in the two groups.

There were no adverse effects of metformin apparent on post hoc safety analyses comparing the proportion of participants with a recordable SAE between the two groups or the combined adverse outcomes of miscarriage, termination of pregnancy, stillbirth or neonatal death (combined adverse outcomes OR 3.597, 95% CI 0.793 to 17.504).

Two participants in the study delivered a stillborn baby. One of the fetuses had a known congenital cardiac defect and developed severe hydrops. The participant went into spontaneous preterm labour at 31 weeks' gestation and the baby was stillborn. The other participant presented with an intrauterine death at 38 weeks' gestation and delivered a stillborn baby weighing 2600 g (< 3rd centile for gestation). Both of the participants were in the metformin group. Neither had any recorded diary entries for tablet taking nor met the adherence criteria for inclusion in the per-protocol analysis.

There were four mid-trimester miscarriages in the metformin group. One was at 20 weeks' gestation following the participant's involvement in a road traffic accident. One was an intrauterine fetal demise detected at the 20-week fetal anomaly scan. Two were spontaneous miscarriages at 18 weeks' gestation, with one of these following a spontaneous rupture of membranes.

Three participants underwent termination of pregnancy following randomisation. One participant was in the metformin group and underwent termination for a fetus with trisomy 21. The other two participants were in the placebo group: one fetus was terminated following a spontaneous rupture of membranes at 18 weeks' gestation and the other because of a fetal anomaly (split hand and foot syndrome).

On per-protocol analysis of these outcomes, only one participant remained eligible for inclusion (one termination of pregnancy in the placebo group).

Adverse outcomes are summarised in *Table 9*.

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TABLE 9 Secondary outcomes: adverse outcomes

	ITT							Per protocol						
	Placebo		Metformin					Placebo		Metformin				
Outcome	*n* (*N*)	%	*n* (*N*)	%	OR	95% CI	*p*-value	*n* (*N*)	%	*n* (*N*)	%	OR	95% CI	*p*-value
Women or their babies with a recorded SAE	41 (222)	18.5	37 (225)	16.4	0.869	0.533 to 1.417	0.573	22 (118)	18.6	14 (109)	12.8	0.643	0.311 to 1.331	0.2767
Maternal outcomes														
Any caesarean section in index pregnancy[a]	76 (222)	34.2	65 (219)	29.7	0.811	0.543 to 1.211	0.306	43 (118)	36.4	31 (108)	28.7	0.702	0.401 to 1.230	0.2566
Primary caesarean section	46 (222)	20.7	42 (219)	19.2	0.908	0.569 to 1.449	0.685	25 (118)	21.2	22 (108)	20.4	0.952	0.500 to 1.811	1.0000
Post-partum haemorrhage > 1000 ml	21 (216)	9.7	20 (212)	9.4	0.967	0.508 to 1.842	0.919	13 (118)	11.0	9 (109)	8.3	0.721	0.295 to 1.763	0.5079
Preterm birth[b]	14 (220)	6.4	18 (214)	8.4	1.345	0.651 to 2.777	0.466	4 (117)	3.4	8 (108)	7.4	2.260	0.661 to 7.732	0.2392
Development of GDM[c]	36 (153)	23.5	26 (142)	18.3	0.728	0.414 to 1.283	0.273	22 (104)	21.2	15 (92)	16.3	0.726	0.351 to 1.501	0.3877
Pregnancy-induced hypertension	14 (222)	6.3	21 (221)	9.5	1.56	0.772 to 3.152	0.22	11 (118)	9.3	11 (109)	10.1	1.092	0.453 to 2.631	0.84
Pre-eclampsia	3 (222)	1.4	7 (221)	3.2	2.39	0.61 to 9.36	0.21	3 (118)	2.5	3 (109)	2.8	1.085	0.214 to 5.493	0.92
Fetal and neonatal outcomes (live births only)														
Admission to the neonatal unit[d]	29 (219)	13.2	14 (213)	6.6	0.461	0.236 to 0.899	0.023	13 (116)	11.2	8 (108)	7.4	0.634	0.252 to 1.595	0.3329
Congenital anomaly[d]	8 (217)	3.7	7 (209)	3.3	0.905	0.322 to 2.543	0.850	4 (115)	3.5	4 (107)	3.7	1.078	0.263 to 4.421	0.9173
Neonatal death in the delivery room[d]	0 (220)	0	0 (214)	0				0 (117)	0	0 (108)	0			
Neonatal death at a later stage[d]	2 (220)	0.91	1 (214)	0.5			1.000	0 (117)	0	0 (108)	0			
Incidence of low birthweight < 10th centile	11 (220)	5.0	14 (214)	6.5	1.330	0.590 to 2.999	0.492	6 (117)	5.1	6 (108)	5.6	1.088	0.340 to 3.482	0.8867
Incidence of low birthweight < 3rd centile[d]	3 (220)	1.4	3 (214)	1.4			1.000	1 (117)	0.9	1 (108)	0.9			1.0000

	ITT							Per protocol						
	Placebo		Metformin					Placebo		Metformin				
Outcome	*n* (*N*)	%	*n* (*N*)	%	OR	95% CI	*p*-value	*n* (*N*)	%	*n* (*N*)	%	OR	95% CI	*p*-value
Maternal symptoms up to 36 weeks' gestation[e]														
Taste disturbance	32 (198)	16.2 (199)	25	12.6	0.745	0.424 to 1.311	0.308	20 (118)	16.9	17 (109)	15.6	0.905	0.447 to 1.835	0.7829
Skin reactions	39 (198)	19.7 (199)	36	18.1	0.900	0.545 to 1.489	0.683	23 (118)	19.5	21 (109)	19.3	0.986	0.510 to 1.905	0.9658
Abdominal pain	42 (198)	21.2 (199)	49	24.6	1.213	0.759 to 1.940	0.419	26 (118)	22.0	32 (109)	29.4	1.471	0.807 to 2.678	0.2074
Flatulence	44 (198)	22.2 (199)	51	25.6	1.206	0.760 to 1.915	0.427	28 (118)	23.7	38 (109)	34.9	1.720	0.964 to 3.069	0.0662
Constipation	57 (198)	28.8 (199)	57	28.6	0.993	0.643 to 1.534	0.975	38 (118)	32.2	37 (109)	33.9	1.082	0.622 to 1.882	0.7805
Diarrhoea	37 (198)	18.7 (199)	83	41.7	3.113	1.975 to 4.908	< 0.0001	24 (118)	20.3	60 (109)	55.0	4.896	2.669 to 8.617	< 0.0001
Nausea	79 (198)	39.9 (199)	97	48.7	1.432	0.962 to 2.132	0.077	46 (118)	39.0	49 (109)	45.0	1.278	0.754 to 2.168	0.3626
Vomiting	43 (198)	21.7 (199)	63	31.7	1.670	1.064 to 2.621	0.026	24 (118)	20.3	34 (109)	31.2	1.775	0.970 to 3.249	0.0626
Headache	66 (198)	33.3 (199)	65	32.7	0.970	0.638 to 1.474	0.887	40 (118)	33.9	37 (109)	33.9	1.002	0.578 to 1.737	0.9941

a Post hoc test.
b Live births only: 4/14 preterm births in the placebo group and 3/18 in the metformin group were spontaneous preterm births following preterm labour.
c IADPSG criteria: fasting glucose ≥ 5.1 mmol/l or 2-hour glucose ≥ 8.5 mmol/l on either visit 4 or visit 6.
d Fisher's exact test reported.
e For all symptoms, categories are none/mild/moderate or severe. If a participant had any symptom at any time this is recorded as 'yes'.

Note
Shading represents data not calculated.

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Chapter 4 Substudies

Maternal and neonatal body composition

Introduction

Body mass index is routinely used as a proxy for adiposity. However, a limitation of BMI is that it makes no distinction between fat mass and FFM and indeed other components of total body weight. BMI has been shown to be well correlated with adiposity in pregnant women, although with a wide CI[34] and a weakening of correlation closer to term.[35] As fat mass is particularly relevant in the context of insulin sensitivity, we aimed to examine the effect of metformin on fat mass specifically, as well as on overall gestational weight change.

The effect of maternal metformin on the body composition of the infant was also of interest in this study. Body composition at birth, which includes fat mass and FFM as opposed to birthweight alone, is probably a more important predictor for long-term risk of disease such as obesity and metabolic syndrome. Whereas FFM is generally a reflection of genetic effects, fat mass is more variable and susceptible to factors that affect fetal growth such as maternal weight gain in pregnancy, maternal obesity and insulin sensitivity.[10,36,37]

There are numerous ways to assess body composition, including underwater weighing, dual-energy X-ray absorptiometry and bioelectrical impedence analysis. These all have limitations, particularly in our two subject groups: pregnant women and infants. Air displacement plethysmography (ADP) is increasingly recognised as the gold standard tool to best assess body composition, particularly in these challenging groups.[38] ADP is based on the principle of Boyle's law, which states that air compressed will decrease in volume proportional to increasing pressure at a constant temperature. The subject is placed inside a sealed chamber of known volume and any change in pressure and volume is attributable to the volume of the subject. The technique is quick and generally acceptable to all, excepting those with severe claustrophobia.

Methods

Maternal fat mass was measured using ADP at baseline, 36 weeks' gestation and 3 months post-partum. Infant fat mass was measured using the same technique within 72 hours of birth and at 3 months of age.

Equipment was used in a temperature-controlled room (21–27 °C) and calibrated at the start of each day of use.

Adult ADP tests were performed with the BOD POD [see www.lifemeasurement.com (accessed 21 June 2016)]. Subjects were fasted and had abstained from exercise for at least 2 hours prior to the test. They were asked to empty their bladder and remove all jewellery and glasses. The test was performed with the subject wearing minimal skintight clothing, for example swimwear, and a hair cap. Subjects were in a resting state.

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Infant ADP tests were performed with the PEA POD (see www.lifemeasurement.com). The infant's clothes and nappy were removed and a head cap applied or hair smoothed. The instrument was calibrated to account for the mass of two hospital identification bracelets and an umbilical cord clip for measurements in the newborn babies.

Statistical analysis

Data are expressed as mean ± SD. Outcomes were analysed using a linear regression model, adjusted by BMI band. Significance was set at $p < 0.05$.

Results

Edinburgh participants only were invited to participate in this substudy. The final cohort numbers following unblinding are provided in *Table 10*.

There were no significant differences in maternal fat mass at baseline, 36 weeks' gestation and 3 months post partum. There was no significant difference in percentage change in maternal fat mass between early and late pregnancy and 3 months post-partum between the placebo group and the metformin group.

There was no significant difference in percentage change in neonatal fat mass from birth to 3 months of age between the placebo group and the metformin group.

Discussion

Metformin taken during pregnancy does not appear to have had an effect on maternal total body fat percentage in late pregnancy or at 3 months post-partum. In the study population as a whole, we did not see any differences in total body weight or skinfold thickness, which would suggest that metformin has not had a significant effect on the distribution of body fat, although the sample size was small. This is supported by our MRI data (see *Magnetic resonance imaging assessment of maternal and fetal adipose distribution*) in which we did not see any significant differences in body fat distribution between the two groups in a smaller cohort of subjects.

There was no significant difference in body fat percentage in the babies, either at birth or at 3 months of age. This is similar to the findings of the metformin compared with insulin for the treatment of gestational diabetes trial,[39] in which there were no differences at birth in birthweight, upper arm circumference, tricep and subscapular skinfold thickness and ponderal index between the babies exposed to metformin and those whose mothers received insulin. However, when these children were assessed again at age 2 years, those who were exposed to metformin had similar total body fat (assessed by dual-energy X-ray absorptiometry) but larger skinfold thickness,[40] suggesting that they had less central fat and may therefore be more insulin sensitive in the longer term. This highlights the need for follow-up studies in our cohort to assess any longer-term effects that metformin exposure may have had on fat distribution in these children.

TABLE 10 Maternal and neonatal body composition

	ITT							Per protocol						
	Placebo		Metformin		Adjusted mean difference			Placebo		Metformin		Adjusted mean difference		
Outcome	Mean (*n*)	SD	Mean (*n*)	SD		95% CI	*p*-value	Mean (*n*)	SD	Mean (*n*)	SD		95% CI	*p*-value
Maternal														
Body mass (kg)														
Baseline	101.39 (47)	16.2	103.32 (53)	16.0				100.53 (27)	12.7	106.66 (33)	17.0			
36 weeks' gestation	108.79 (31)	14.9	113.37 (30)	15.9				106.92 (22)	10.7	112.95 (29)	16.9			
3 months post-partum	102.82 (29)	12.8	106.47 (30)	14.8				102.72 (21)	13.7	107.63 (27)	16.2			
Fat mass (kg)														
Baseline	47.93 (48)	12.1	50.32 (53)	11.9	1.212	–2.111 to 4.535	0.4708	46.68 (27)	9.2	52.12 (33)	12.2	2.578	–1.160 to 6.316	0.1727
36 weeks' gestation	50.83 (31)	10.9	54.37 (30)	12.2	1.852	–2.623 to 6.327	0.4108	48.98 (22)	8.1	54.15 (29)	12.3	3.225	–1.510 to 7.960	0.1773
3 months post-partum	49.06 (29)	9.0	50.09 (30)	13.7	–0.002	–5.227 to 5.223	0.9994	48.39 (21)	9.5	50.47 (27)	13.4	0.805	–5.196 to 6.806	0.7883
Fat (%)														
Baseline	46.82 (48)	5.6	48.19 (53)	5.2				46.21 (27)	5.2	48.56 (33)	5.0			
36 weeks' gestation	46.30 (31)	4.8	47.48 (30)	4.6				45.55 (22)	4.7	47.44 (29)	4.7			
3 months post-partum	47.45 (29)	5.0	48.35 (30)	5.3				46.78 (21)	5.0	48.49 (27)	4.8			
Fat mass % change from baseline to 36 weeks[a]					–2.461	–7.034 to 2.111	0.2852					–3.844	–8.888 to 1.201	0.1319
Fat mass % change from baseline to 3 months post-partum[a]					–5.078	–13.052 to 2.896	0.2069					–5.203	–13.97 to 3.57	0.2382

continued

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TABLE 10 Maternal and neonatal body composition (*continued*)

Outcome	ITT							Per protocol						
	Placebo		Metformin		Adjusted mean difference	95% CI	*p*-value	Placebo		Metformin		Adjusted mean difference	95% CI	*p*-value
	Mean (*n*)	SD	Mean (*n*)	SD				Mean (*n*)	SD	Mean (*n*)	SD			
Neonatal														
Body mass (kg)														
Birth	3.40 (22)	0.5	3.38 (21)	0.4				3.49 (15)	0.5	3.38 (20)	0.4			
3 months	9.68 (30)	19.4	6.01 (28)	0.9				6.24 (22)	0.8	6.07 (25)	0.9			
Fat mass (kg)														
Birth	0.46 (22)	0.05	0.45 (21)	0.2	–0.010	–0.152 to 0.133	0.8905	0.49 (15)	0.3	0.45 (20)	0.2	–0.073	–0.237 to 0.091	0.3727
3 months	1.60 (30)	0.08	1.44 (29)	0.08	–0.164	–0.398 to 0.070	0.1660	1.61 (22)	0.5	1.44 (26)	0.5	–0.192	–0.459 to 0.076	0.1556
Fat (%)														
Birth	12.08 (22)	5.7	12.86 (21)	4.5				13.45 (15)	5.8	12.77 (20)	4.6			
3 months	25.88 (31)	6.1	23.19 (29)	5.9				25.80 (22)	5.9	23.33 (26)	5.7			
Fat mass % change from birth to 3 months[a]					–0.220	–0.606 to 0.165	0.2511					–0.253	–0.671 to 0.165	0.2235

a When suitable paired observations are present.

Hyperinsulinaemic–euglycaemic clamp study

Introduction

Normal pregnancy is associated with marked changes in insulin sensitivity, glucose homeostasis and lipid and protein metabolism. In early pregnancy, fasting glucose decreases by 0.11 mmol/l with little further decrease by the end of pregnancy.[41] Insulin secretion increases but insulin sensitivity remains unchanged.[42,43] This promotes lipogenesis to prepare for the rising energy needs of pregnancy and also to allow lipid storage in preparation for the energy demands of lactation. Glucose tolerance is normal at this stage, as is peripheral insulin sensitivity and hepatic basal glucose production.[43–45] By mid-pregnancy, despite the increase in insulin secretion, basal hepatic glucose production also increases, as does total gluconeogenesis, to meet the increasing demands of the fetoplacental unit.[46–48] By late gestation, peripheral insulin sensitivity is markedly decreased such that insulin is unable to suppress lipolysis, allowing an increase in free fatty acids and therefore more energy available for gluconeogenesis.[49] Overall, the insulin sensitivity of late pregnancy is reduced by 50–70% compared with the non-pregnant state. These mechanisms are important to ensure a ready supply of energy substrates for the developing fetus.

In obese pregnant individuals, these mechanisms are disordered. Obesity is associated with a state of diminished insulin sensitivity and so obese women enter pregnancy already resistant to insulin. The reduction in fasting glucose in very early pregnancy is diminished or absent.[41] By late gestation, a physiological reduction in peripheral insulin sensitivity by 15% has been demonstrated.[50] In addition, there is marked hepatic insulin resistance with reduced insulin-mediated glucose disposal and a reduction in insulin-stimulated suppression of endogenous glucose production (EGP).[51] Thus, there may be an excess of free fatty acids and glucose, which are freely transferred across the placenta and may potentially drive fetal overgrowth and programming of later-life insulin resistance. However, our own work[52] has demonstrated differences between lean and severely obese pregnant women only at early and mid-gestation, with a convergence in degree of insulin resistance by late pregnancy.

This mechanistic substudy was designed to examine the effect of metformin on insulin resistance in obese pregnancy. We used the gold standard method of assessing insulin sensitivity, the hyperinsulinaemic–euglycaemic clamp, to assess this in a subgroup of women participating in the trial and who were adherent to treatment. To our knowledge, this is the first study to have employed this technique to examine the effect of metformin in pregnant women. The characteristics of the women were similar to those of the women in the study overall. Importantly, those with GDM were excluded.

Methods

Solutions of 6,6–$^{2}H_2$-glucose (d_2-glucose) and 1,1,2,3,3–$^{2}H_5$-glycerol (d_5-glycerol) (Cambridge Isotope Laboratories, Inc., Andover, MA, USA) and soluble insulin (Actrapid®, NovoNordisk, Bagsvaerd, Denmark) were prepared in 0.9% saline.

Participants ($n = 21$) attended the clinical research facility at 08.00 after fasting overnight for 8–10 hours. A 44-mm 20-gauge cannula was inserted into the superficial vein in the dorsum of one hand and kept patent with a slow infusion of 0.9% saline. This hand was wrapped in an electric heated blanket to arterialise the venous blood for sample collection. A second cannula was placed in the antecubital fossa vein of the contralateral arm for the infusates. We infused d_2-glucose (prime 25 µmol/kg then continuous infusion of 22 µmol/kg/hour) and d_5-glycerol (prime 1.6 µmol/kg then continuous infusion of 6.6 µmol/kg/hour) for 5.5 hours. Four steady-state blood samples were taken at 10-minute intervals at the end of three time periods: (1) 60, 70, 80 and 90 minutes; (2) 180, 190, 200 and 210 minutes; and (3) 300, 310, 320 and 330 minutes with infusion of (1) tracers only (no insulin); (2) 20 mU/m^2/minute of insulin (to suppress lipolysis and EGP); and (3) 40 mU/m^2/minute of insulin (to stimulate glucose uptake). Following commencement of the insulin infusion at 90 minutes, blood samples were obtained every 5 minutes from the sampling cannula for measurement of whole blood glucose concentration using an Accu-Chek® blood glucose monitor (Roche Products Ltd, Welwyn Garden City, UK). A solution of 20% dextrose was infused as required to maintain arteriolised blood glucose between 4.5 and 5.5 mmol/l. Additional blood samples were obtained

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every 30 minutes from 90 minutes onwards using fluoride oxalate anticoagulant for formal enzymatic measurement of plasma glucose. The steady-state blood samples for analysis of the tracers and those for insulin and NEFAs were collected on ice, the plasma separated by centrifugation and plasma aliquots stored at –80 °C.

The volume of dextrose infused during the final 30 minutes of the high-dose hyperinsulinaemic–euglycaemic clamp divided by the corresponding insulin concentration at steady state was used to derive the glucose disposal per unit plasma insulin or M/I.

Steele's equation for steady state was applied to calculate the rate of appearance (Ra) or rate of disappearance (Rd) of the tracee (d_2-glucose or d_5-glycerol):

$$\text{Ra} = \text{Rd} = (\text{F}/\text{TTR plasma tracer} - \text{F}), \quad (1)$$

where F is the infusion rate of the tracer and TTR is the tracer-to-tracee ratio.

Endogenous glucose production was calculated by subtracting the variable glucose infusion rate from the calculated Ra glucose. Data from glucose infusion studies were corrected for background ^{13}C enrichment. No exogenous unlabelled glycerol was infused and the abundance of other isotopic species within the tracer infusion is negligible; therefore, corrections were not applied in the calculation of Ra glycerol.

Mass spectrometry analysis

Standard curves were prepared for concentrations of glucose, glycerol, d_2-glucose and d_5-glycerol in plasma with internal standards of $^{13}C_6$-glucose (Isotec, Southport, UK) and butanetriol as previously described.[53] Standard enrichment curves for glucose and glycerol with d_2-glucose and d_5-glycerol, respectively, were also prepared. Briefly, samples and standards were prepared in acetonitrile (Sigma Aldrich, Gillingham, Dorset, UK), internal standards were added and incubated for 20 minutes, extracts were collected under vacuum and eluates were dried and incubated with pyridine/acetate anhydride [200 µl, 1 : 1 volume per volume (v/v)] before drying again and reconstituting in 5% acetic anhydride in heptane. These were analysed on a Quantum Ultra GC-MS/MS, operated using Xcalibur™ software version 3.0.63 (ThermoFisher Scientific; Hemel Hempstead, UK) using a HP-INNOWax column (30 m × 0.32 mm × 0.25 µm; Agilent Technologies Ltd, Stockport, UK). Monitored ions were the glycerol triacetate *m/z* 217, d_5-glycerol triacetate *m/z* 222, butanetriol triacetate *m/z* 231 (internal standard), glucose pentacetate *m/z* 287, d_2-glucose pentacetate *m/z* 289 and $^{13}C_6$-glucose pentacetate *m/z* 293 (internal standard).

Treatment adherence was measured by determining metformin in plasma using an Aria-TSQ Quantum LC-MS/MS liquid chromatography tandem mass spectrometer (ThermoFisher Scientific). Metformin was extracted from plasma (100 µl) using a SLE+ plate (Biotage GB, Ystrad Mynach, UK) following enrichment with d_6-metformin (200 ng) as an internal standard. Calibration standards ranged from 0.5 to 1000 ng of metformin. Analytes were eluted, reduced to dryness under nitrogen (40 °C) and reconstituted in water/acetonitrile (100 µl; 80 : 20 v/v). Chromatographic separation was achieved using an Aria CTC autosampler and Allegros pump on an ACE® Excel™ Super2C18 column (100 × 3 mm; 2 µm; HiChrom, Reading, UK) protected by a Kinetex KrudKatcher® (Phenomenex, Macclesfield, UK) and detected on a TSQ™ Quantum Discovery triple quadrupole mass spectroscopy (ThermoFisher Scientific) operated by selective reaction monitoring in positive electrospray ionisation mode (300 °C, 3 kV). The mobile phase was 0.1% formic acid in water (A), 0.1% formic acid in acetonitrile (B) at a flow rate of 0.2 ml/minute at 30 °C. Gradient elution was achieved by increasing the percentage of acetonitrile from 20% to 90% over a 5-minute run time. Metformin and its isotopically labelled internal standard eluted at 2.1 minutes. Transitions monitored for were *m/z* 130.1 → 60.1 and 71.1 and *m/z* 136.2 → 60.1 and 71.1 for metformin and internal standard, respectively. Linear regression analysis of calibration standards, calculated using peak area ratios of metformin to internal standard, was used to determine the concentration of metformin in the samples.

Statistical analysis

Data are expressed as mean ± standard error of the mean unless otherwise stated. Comparisons were made between groups using an unpaired Student's *t*-test. HOMA-IR data were log-transformed to achieve a normal distribution and the results back transformed for reporting. Significance was set at $p < 0.05$. No adjustment was made for multiple comparisons.

Intravenous access failed in one subject and the procedure had to be abandoned. Hence, data were obtained from 20 of the 21 subjects who attended for a clamp study. Clamp studies were performed blind to treatment allocation, with unblinding revealing that final cohort numbers were as follows: placebo group, $n = 11$; metformin group, $n = 9$. All subjects were compliant with their study medication according to diary entries. One subject in the metformin group did not have detectable levels of metformin in her blood at 36 weeks' gestation and her data were, therefore, excluded from the analysis. Hence the final sample size was 11 women in the placebo group and 8 women in the metformin group.

Results

Participant characteristics

Participant characteristics are shown in *Table 11*.

Effect of metformin on indices of insulin sensitivity for glucose metabolism at 36 weeks' gestation

Mean plasma glucose and insulin concentrations achieved for the two groups are shown in *Figures 3* and *4*.

Whole-body glucose disposal (WGD) was calculated in mg of glucose per kg of FFM per minute at steady state during the high-dose clamp. WGD is an indirect measure of whole-body insulin sensitivity, with a greater glucose disposal rate implying greater insulin sensitivity. The M/I was also calculated to correct for slight differences in achieved plasma insulin in each group and expressed in units of mg of glucose per kgFFM per minute.

Glucose disposal per unit plasma insulin but not WGD was higher in the metformin group than in the placebo group (difference between means 0.02 mg/kgFFM/minute, 95% CI 0.001 to 0.03 mg/kgFFM/minute; $p = 0.04$; and 0.78 mg/kgFFM/minute/μIU/l, 95% CI –0.12 to 1.67 mg/kgFFM/minute/μIU/l; $p = 0.08$, respectively).

In contrast, HOMA-IR scores for these individuals at baseline were similar in the two groups (difference between means –0.87, 95% CI –3.31 to 1.57; $p = 0.46$).

TABLE 11 Participant characteristics in the hyperinsulinaemic euglycaemic clamp substudy

Characteristic	Placebo ($n = 11$)	Metformin ($n = 8$)
Age (years), mean (SD)	29.6 (3.6)	32.6 (3.7)
Nulliparity, *n* (%)	5 (45)	3 (38)
BMI at baseline (kg/m^2), mean (SD)	35.7 (3.5)	38.5 (4.4)
Body fat at time of clamp (%), mean (SD)	46.2 (5.3)	49.1 (3.9)
Gestation at time of clamp (days), mean (SD)	56.25 (4.8)	57.55 (4.2)

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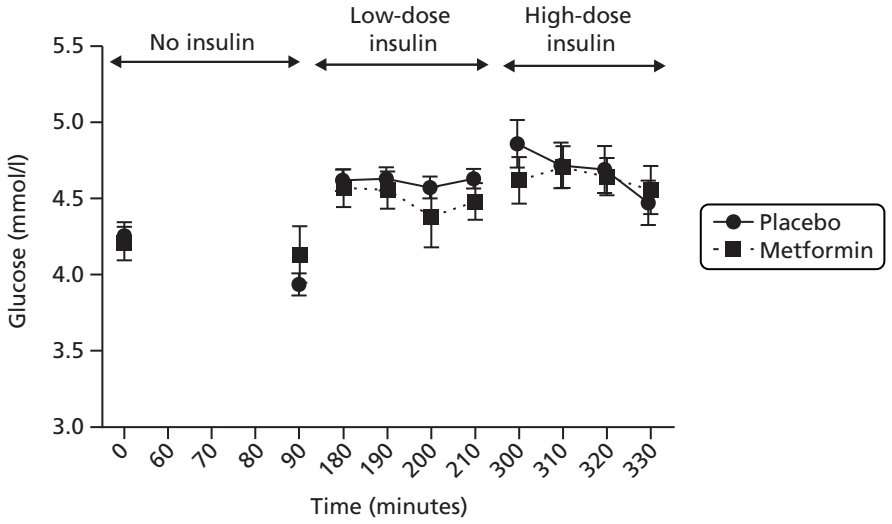


FIGURE 3 Clamped plasma glucose.

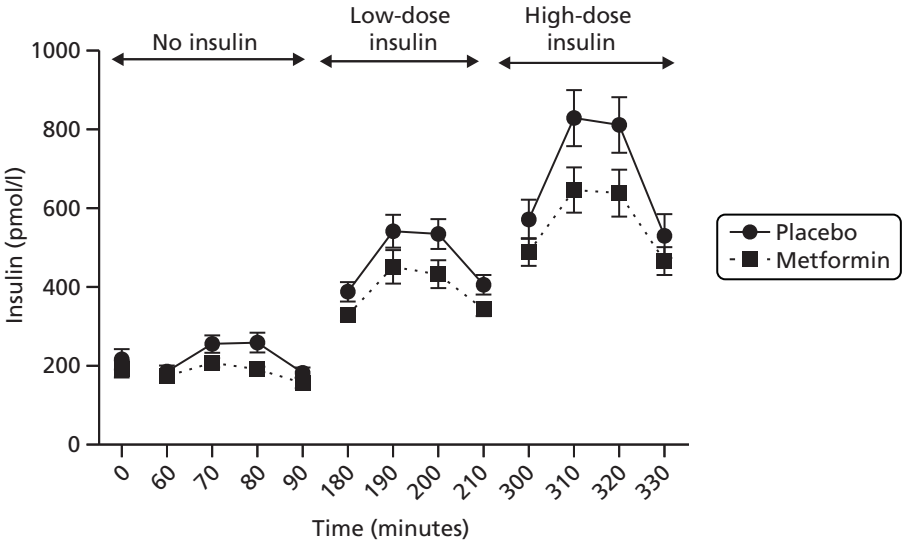


FIGURE 4 Clamped plasma insulin.

In the absence of insulin, EGP (expressed as both milligrams of glucose per kilogram of total body weight per minute and as milligrams of glucose per kilogram of FFM per minute) was greater in the metformin group than in the placebo group (difference between means 0.54 mg/kgFFM/minute, 95% CI 0.08 to 1.00 mg/kgFFM/minute; $p = 0.02$) (*Figure 5*). During low-dose insulin infusion, EGP was again higher in the metformin group (difference between means 0.43 mg/kgFFM/minute, 95% CI 0.02 to 0.84 mg/kgFFM/minute; $p = 0.04$) (see *Figure 5*). There was no significant difference in the percentage suppression from basal EGP to EGP during low-dose hyperinsulinaemic–euglycaemic clamp between the two groups (difference between means 2.89%, 95% CI –7.65% to 13.42%; $p = 0.57$) (see *Figure 5*).

At baseline, prior to insulin infusion, the Rd of glucose and EGP should be equivalent as they are in steady state. The Rd was also significantly greater in the metformin group than the placebo group during the low-dose insulin phase of the clamp (difference between means 0.36 mg/kgFFM/minute, 95% CI 0.22 to 1.18 mg/kgFFM/minute; $p = 0.07$). At high-dose insulin infusion, Rd was increased further but there was no significant difference between the treatment groups (difference between means 0.35 mg/kgFFM/minute, 95% CI –0.79 to 1.50 mg/kgFFM/minute; $p = 0.52$) (*Figure 6*).

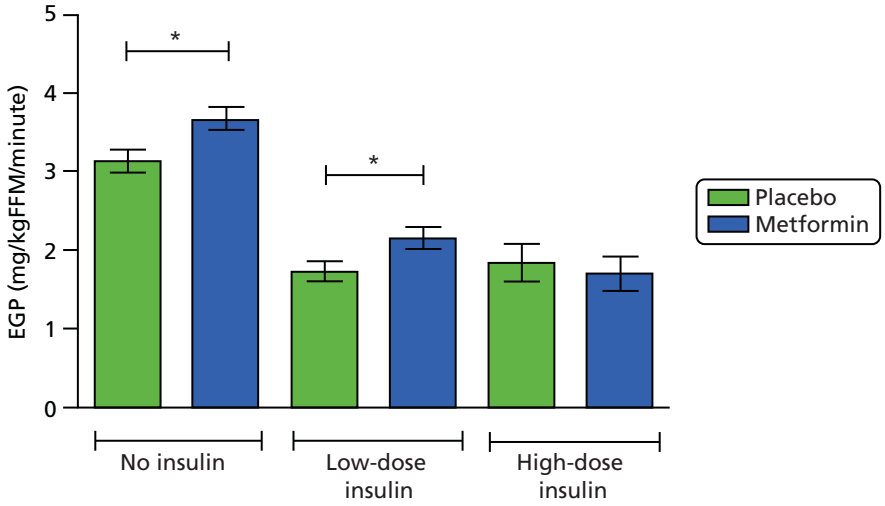


FIGURE 5 Endogenous glucose production. *$p \leq 0.05$.

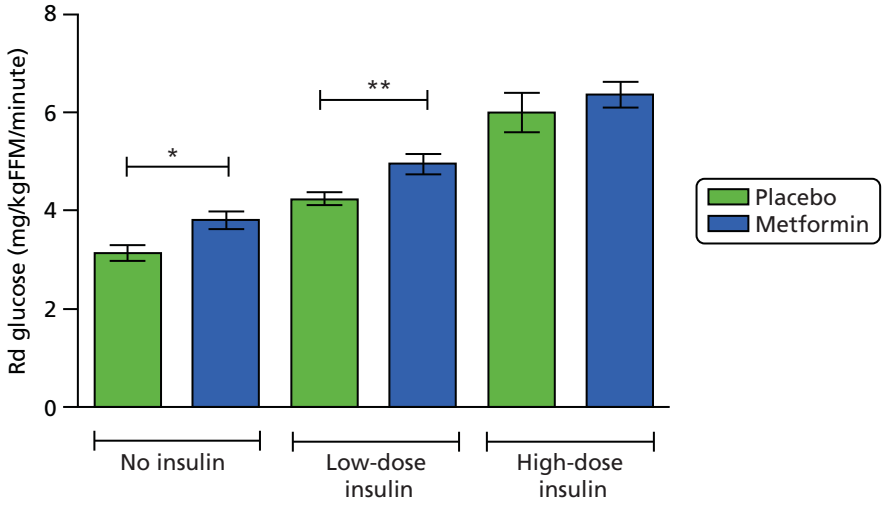


FIGURE 6 Rate of disappearance of glucose. *$p \leq 0.05$; **$p \leq 0.01$.

Effect of metformin on insulin sensitivity for lipolysis at 36 weeks' gestation

Mean plasma glycerol and NEFA concentrations achieved for the two groups are shown in *Figures 7* and *8*. Glycerol turnover per kgFFM is shown in *Figure 9*. There was no difference in glycerol turnover between the metformin and placebo groups (difference between means: no insulin 0.03 mg/kgFFM/minute, 95% CI –0.12 to 0.18 mg/kgFFM/minute; $p = 0.67$; low-dose insulin 0.02 mg/kgFFM/minute, 95% CI –0.06 to 0.10 mg/kgFFM/minute; $p = 0.64$; high-dose insulin –0.01 mg/kgFFM/minute, 95% CI –0.10 to 0.08 mg/kgFFM/minute; $p = 0.87$). Low-dose insulin infusion resulted in suppression of the Rd of glycerol in both groups; high-dose insulin resulted in no further suppression of Rd in either group. There was no difference in serum NEFAs between the groups at any time.

Discussion

We hypothesised that administration of metformin to obese pregnant women would improve insulin sensitivity in the third trimester. These data show that, as expected, subjects taking metformin demonstrated a greater M/I, which is associated with increased insulin sensitivity. The Rd of glucose was enhanced in the metformin-treated group suggesting improved peripheral insulin sensitivity. However, EGP was higher in the metformin-treated subjects, suggesting that, if anything, those on metformin exhibited a reduced ability to suppress hepatic glucose production in response to insulin and enhanced glucose release on fasting. This is perhaps surprising given that metformin is thought to exert its action principally via the

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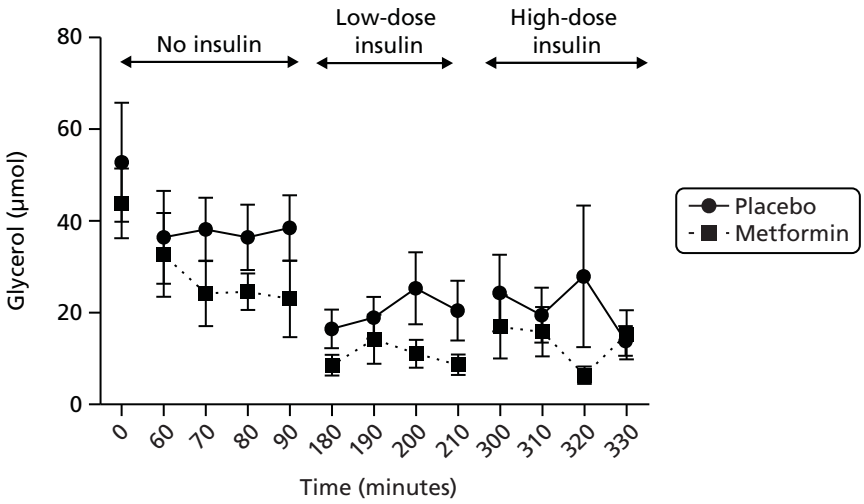


FIGURE 7 Clamped plasma glycerol.

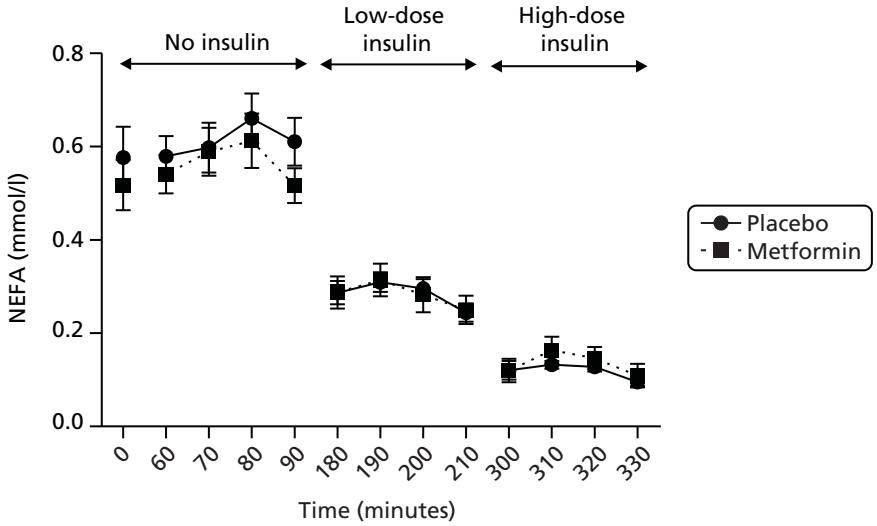


FIGURE 8 Clamped plasma NEFAs.

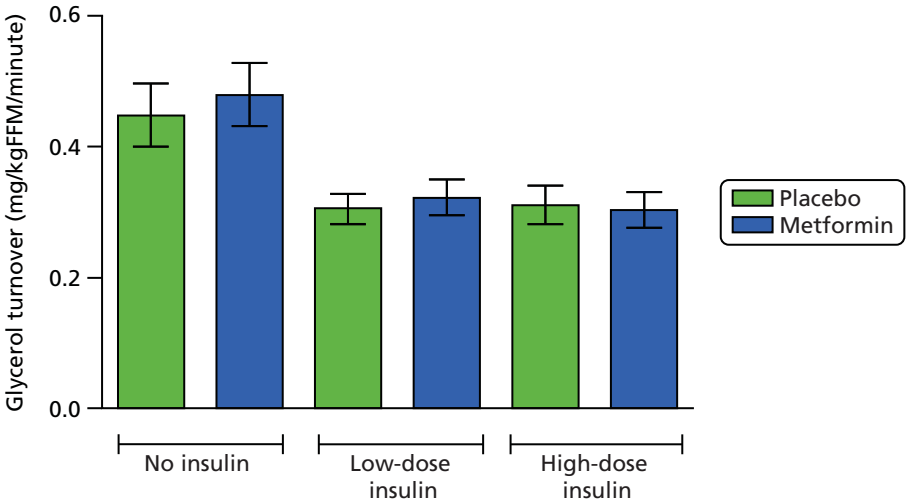


FIGURE 9 Glycerol turnover.

liver, inhibiting gluconeogenesis and reducing hepatic glucose production,[54] although an effect mediated via peripheral glucose disposal has also been shown.[55,56] Additionally, metformin has recently been shown to stimulate EGP in healthy fasting individuals who are not pregnant.[57] Metformin's mechanism of action in pregnant women has, to our knowledge, never been studied. These data suggest enhanced glucose flux in the metformin-treated women (i.e. higher liver production and higher peripheral disposal of glucose). Interpretation of this is perhaps complicated by the presence of the fetoplacental unit, which represents a significant proportion of the FFM at 36 weeks' gestation and must account for uptake of some of the glucose. These data confirm that the hyperinsulinaemic–euglycaemic clamp is a more sensitive measure of insulin resistance as we demonstrated differences in M/I and EGP but not in HOMA-IR score.

The lipolytic pathway was equally sensitive to exogenous insulin in both the metformin- and the placebo-treated groups. Maximal suppression (around 70%) was achieved by low-dose insulin, with no further suppression at the high-dose infusion. Enhanced rates of lipolysis are thought to be important towards the end of normal pregnancy to provide maternal substrates for gluconeogenesis and triglyceride synthesis and spare glucose to facilitate normal fetal growth. Reduced third-trimester lipolysis is associated with fetal growth restriction[58] and so these data are perhaps reassuring on the safety of metformin in pregnancy in terms of not increasing the risk of intrauterine growth restriction.

In conclusion, these substudy data confirm that metformin can improve insulin sensitivity in obese pregnant women. However, this may be offset by increased glucose flux and hence there is a lack of effect on fetal nutrition or growth. Additionally, metabolism at 36 weeks' gestation may not reflect metabolism in mid-gestation, when differences between lean and obese women are greater.

Endothelial function

Introduction

Hypertensive disorders are more prevalent in obese populations[59] including those who are pregnant.[60] Obese women are at greater risk of chronic hypertension, pregnancy-induced hypertension and pre-eclampsia:[61–64] for a woman with a BMI of > 35 kg/m^2, the risk of pre-eclampsia is twice that of a normal lean woman.[65] The causal mechanisms behind these associations are not clear but insulin resistance may play a role. Women with diabetes mellitus of all types during pregnancy have a heightened risk of pre-eclampsia and women with pre-eclampsia have an increased risk of type 2 diabetes mellitus in later life.[66] Other possible contributory mechanisms include endothelial dysfunction, inflammation, dyslipidaemia and oxidative stress, all of which are associated with both obesity and pre-eclampsia.[67–69]

The vascular endothelium is the layer of endothelial cells between the blood vessel wall and the bloodstream. It is a key regulator of vascular homeostasis, acting not only as a barrier but also as an active signal transducer for circulating influences that modify the vessel wall tone and phenotype.[70] Endothelial dysfunction is characterised by a shift of the actions of the endothelium towards reduced vasodilatation and a more pro-inflammatory and pro-thrombotic state.[71] Mechanisms that participate in the reduced vasodilatory responses include reduced nitric oxide bioavailability and oxidative stress.[71] Endothelial dysfunction is associated with most forms of cardiovascular disease, such as hypertension, coronary artery disease, diabetes and chronic renal failure, and often precedes their clinical manifestations.[72] It has also been demonstrated in disease states in the absence of overt cardiovascular complications, such as the metabolic syndrome[73] and obesity.[74]

Endothelial dysfunction in pregnancy has been most widely studied in the context of pre-eclampsia, in which impaired maternal vascular function has been reported.[75] GDM is associated with increased oxidative stress and overexpression of inflammatory cytokines, both of which contribute to endothelial dysfunction.[76] Obesity in pregnancy shares these features and impaired endothelial function has been demonstrated in obese pregnant women.[67,77] Given that insulin resistance and hyperglycaemia are linked to inflammation, vascular dysfunction and hypertension, these processes are potential mediators for these upstream causative pathways, linking endothelial dysfunction with cardiovascular disease in obese pregnant women.

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Metformin might be the ideal agent to address and reverse these abnormalities in obese pregnant women. In addition to its primary function as an insulin-sensitising agent, metformin has beneficial effects on the vascular endothelium, lipid profile and oxidative stress.[78,79] These effects appear to be independent of metformin's glucose-lowering and insulin-sensitising effects. Metformin also improves vascular function in a variety of clinical syndromes associated with insulin resistance, for example reducing cardiovascular disease risk in patients with type 2 diabetes mellitus[80] and improving endothelial function in patients with type 1 diabetes mellitus, metabolic syndrome and PCOS.[79,81–83]

Nested within the EMPOWaR trial, this mechanistic substudy was designed to test the hypothesis that, compared with those taking placebo, participants treated with metformin would demonstrate improved endothelial function in late pregnancy.

Methods

We recruited a subset of women participating in the EMPOWaR trial. The characteristics of participants in the substudy were similar to the characteristics of those in the EMPOWaR trial overall. Importantly, those with GDM were excluded. We also included a comparator 'control' group of lean pregnant subjects who, with the exception of BMI, were matched for baseline characteristics to the EMPOWaR study population. Participants of the EMPOWaR trial were assessed at 12–16 weeks' gestation following randomisation but prior to commencing study treatment and at around 36 weeks' gestation while receiving trial medication. All measurements were performed blind to treatment allocation. Lean control subjects were assessed at both 12–16 and 36 weeks' gestation.

Endothelial function

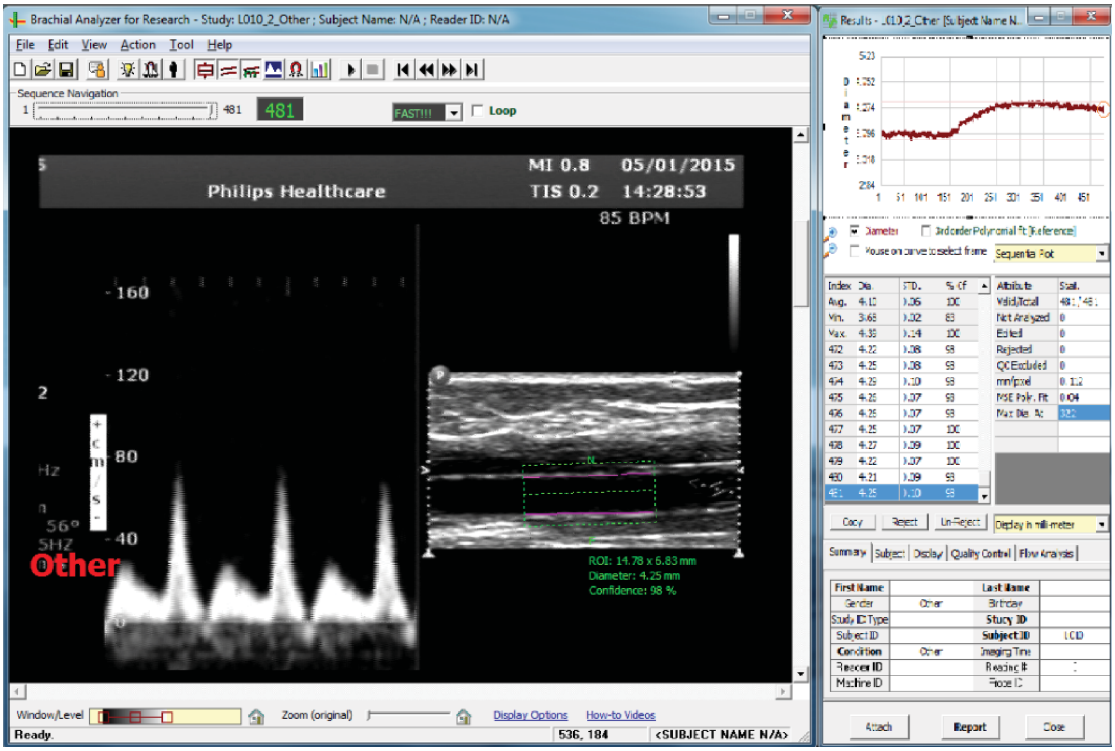
We assessed endothelial function by measuring FMD in the brachial artery. Subjects were asked to refrain from eating, smoking or consuming alcohol or caffeine in the preceding 4 hours. Measurements were obtained in a temperature-controlled room with the subject resting in a semi-recumbent position on a bed. Subjects in late pregnancy had a left lateral tilt applied to avoid aortocaval compression.

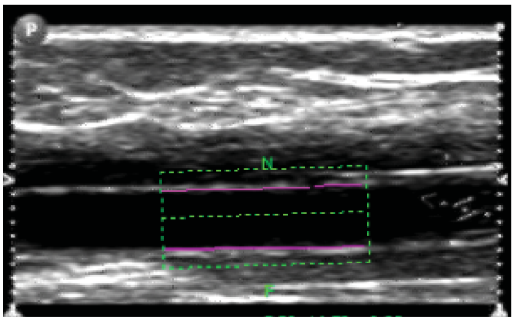
Measurements were made using ultrasound imaging (CX50 Ultrasound system with a 7-MHz linear array transducer; Philips Medical Systems, Guildford, UK) of the brachial artery, 2–5 cm above the antecubital fossa. A baseline rest image was acquired for a period of 60 seconds. Arterial occlusion was performed using a sphygmomanometric cuff applied below the antecubital fossa, inflated to suprasystolic pressure for 5 minutes and then released to induce hyperaemia. The brachial artery ultrasound was recorded for 30 seconds before and 5 minutes after cuff deflation. Images were acquired with electrocardiogram gating, with measurements made in end-diastole, corresponding to the onset of the R wave. To minimise movement, the scan probe was held in place with a probe-retaining device throughout the period of the study. Images were stored digitally and measurements made using edge-detection software [Vascular Research Tools 5; Medical Imaging Applications LLC, see www.mia-llc.com (accessed 24 June 2016)] (*Figure 10*).

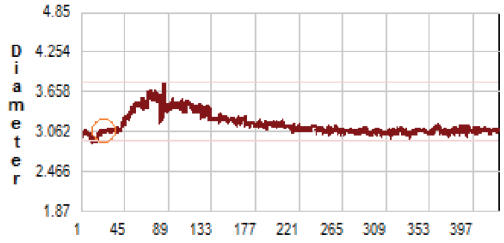
The results were expressed as change in arterial diameter (D) divided by baseline diameter:

$$\text{FMD}\ (\%) = \left(\frac{D_{\text{peak}} - D_{\text{baseline}}}{D_{\text{baseline}}}\right) \times 100. \qquad (2)$$

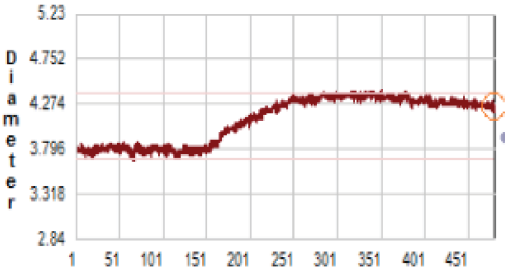
The peak diameter (D_{peak}) was taken as the mean of the diameter measurements taken 5 seconds either side of the peak diameter. The baseline diameter (D_{baseline}) was taken as the mean of the 60 seconds of baseline recording. We then measured endothelium-independent vasodilatation. After 10 minutes of rest, a second baseline image was obtained for 60 seconds and then a single low dose (25 µg) of sublingual nitroglycerin (GTN) spray was given and measurement recorded for 5 minutes. Again, the baseline diameter was taken as the mean of the first 60 seconds and the peak diameter was taken as the mean of the measurements 5 seconds either side of the peak.







FMD response



GTN response

FIGURE 10 Representative images from analysis software.

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Statistical analysis

Graphical data are presented as mean ± standard error of the mean. Comparisons between placebo, metformin and lean groups at both time points were made using one-way ANOVA. Two-way ANOVA was used to examine differences over time in the various treatment groups. Comparisons between early and late pregnancy within groups were made using Student's unpaired *t*-tests. Significance was taken as a two-sided *p*-value of < 0.05.

Results

Forty-one eligible women in the EMPOWaR study agreed to participate in the substudy. However, the majority of EMPOWaR participants were unable or unwilling to attend for the two study visits: only one woman in the placebo group and two in the metformin group attended both visits. In contrast, all women in the lean control group attended both visits except for one lean subject who was ineligible at 36 weeks' gestation because of a preterm birth. Images from nine subjects had to be discarded as they were of insufficient quality for analysis. The final study population (*Table 12*), therefore, included 28 subjects ($n = 6$ placebo, $n = 12$ metformin and $n = 10$ lean) at 12–16 weeks' gestation and 26 subjects ($n = 8$ placebo, $n = 9$ metformin and $n = 9$ lean) at 36 weeks' gestation. Data are presented for 28 subjects at baseline and 25 subjects at 36 weeks' gestation.

There were no differences in FMD between the placebo, metformin and lean groups at baseline or at 36 weeks' gestation (one-way ANOVA: baseline, $p = 0.88$; 36 weeks, $p = 0.89$) (*Figure 11*; see also *Table 12*). There was a decline in endothelial function in late pregnancy compared with early pregnancy across all groups (two-way ANOVA $p = 0.03$). There were no differences in endothelium-independent vasodilatation between groups or within groups in early and late pregnancy (see *Table 12* and *Figure 11*).

TABLE 12 Endothelial function substudy cohort characteristics and results

Characteristics	Placebo ($n = 13$)	Metformin ($n = 19$)	Lean ($n = 10$)
Age (years), mean (SD)	31.5 (4.4)	27.3 (6.1)	35.6 (4.1)
Nulliparity, %	46.7	68.8	70
Current smoking, %	6.7	18.8	0
BMI baseline (kg/m^2), mean (SD)	38.4 (4.9)	37.7 (5.7)	23.05 (3.5)
SBP baseline (mmHg), mean (SD)	121.7 (10.8)	117.3 (9.7)	109.9 (15.4)
DBP baseline (mmHg), mean (SD)	69.1 (7.3)	69.1 (9.5)	65.9 (10.3)
SBP late pregnancy (mmHg), mean (SD)	123.2 (9.1)	118.0 (15.3)	123.8 (11.0)
DBP late pregnancy (mmHg), mean (SD)	75.0 (6.0)	70.4 (8.5)	73.8 (9.6)
Mean gestation at time of study (days), mean (SD)			
Baseline	100.2 (10.5)	105.2 (7.7)	100.3 (7.7)
Late pregnancy	252.1 (4.7)	253.3 (6.8)	257.0 (5.6)
FMD, % [*n*] (SD)			
Baseline	10.16 [6] (5.0)	8.58 [12] (6.9)	10.22 [10] (10.6)
Late pregnancy	6.08 [8] (5.3)	5.10 [9] (4.0)	5.40 [9] (3.0)
GTN-mediated dilatation, % [*n*] (SD)			
Baseline	12.74 [6] (9.7)	9.07 [12] (5.6)	11.98 [10] (9.0)
Late pregnancy	11.04 [8] (8.1)	9.61 [8][a] (4.4)	8.50 [9] (4.0)

DBP, diastolic blood pressure; SBP, systolic blood pressure.
a One GTN image had to be discarded as it was of insufficient quality to analyse.

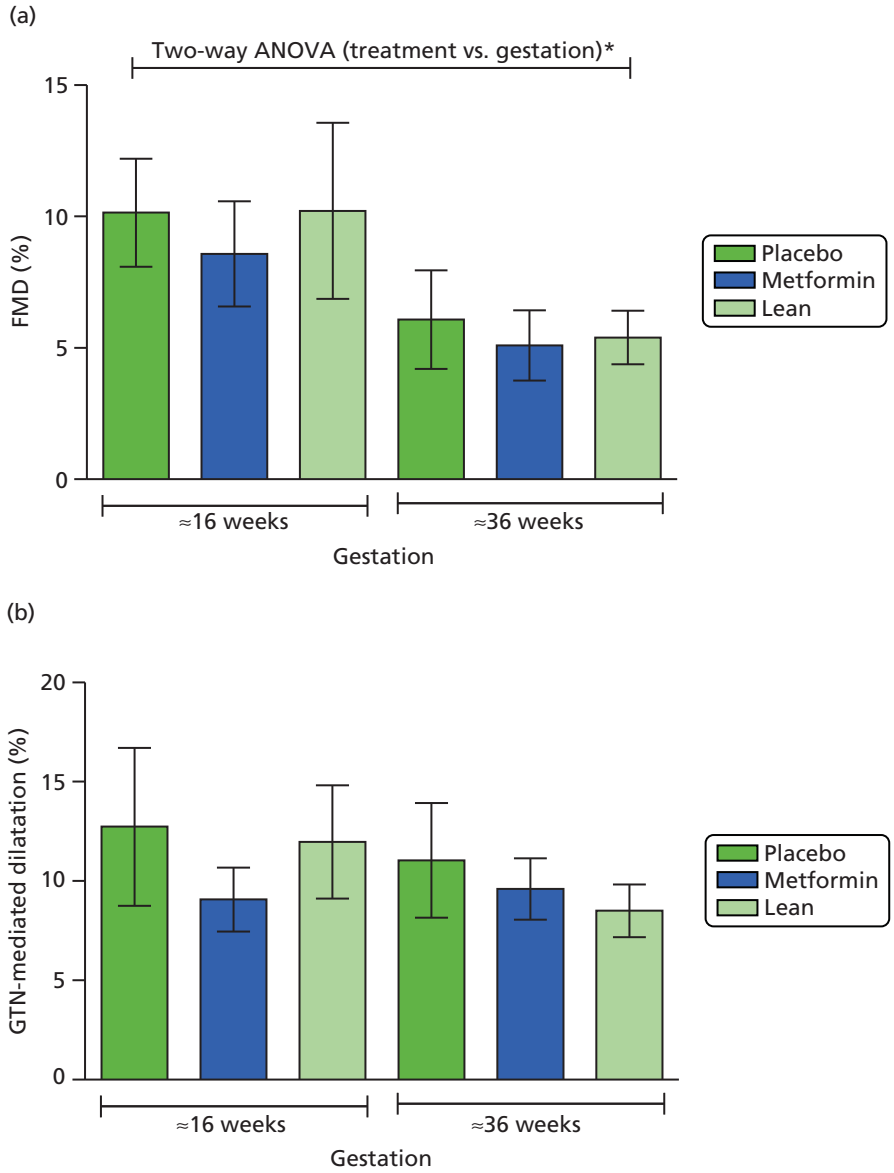


FIGURE 11 (a) FMD and (b) GTN-mediated dilatation. *$p \leq 0.05$.

Discussion

We have used flow-mediated vasodilatation, the gold-standard non-invasive method of assessing endothelial function, in obese and lean pregnant women as part of the EMPOWaR study. Although we demonstrated a selective gestation-associated decline in endothelium-dependent vasodilatation, we saw no differences in endothelial function across obese and lean groups, nor any effect of the treatment intervention metformin. This suggests that pregnancy is associated with altered endothelial function and this is independent of body weight or glucose sensitivity.

There was a decline in endothelial function between early and late pregnancy in participants in all three groups. This is contrary to the finding of one longitudinal study of endothelial function in eight normal-weight women that demonstrated increasing FMD across the three trimesters of pregnancy.[84] However, a much larger study of 157 normal-weight pregnant women demonstrated an increase in FMD in pregnant compared with non-pregnant subjects, apparent from 10 weeks' gestation, but a progressive decline in FMD to pre-pregnancy levels from around 30 weeks' gestation, in keeping with our data in both lean and obese participants.[85]

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To our knowledge, this is the first study of the effect of metformin on endothelial function in pregnant women. It is not clear why metformin does not appear to have had an effect on the vascular endothelium in the study population when this has been demonstrated in other insulin-resistant populations. Pregnancy is associated with major vascular and haemodynamic changes, the primary event probably being a fall in peripheral vascular resistance.[86] This is most likely mediated by endothelium-dependent factors including nitric oxide synthesis upregulation by oestradiol and possibly vasodilatory prostaglandins.[87–89] The consequent fall in systemic vascular resistance leads to a compensatory increase in cardiac output. Larger vessels dilate less than smaller ones.[90] It is possible that the increased vessel diameter of pregnancy, along with stimulated nitric oxide activity of pregnancy, may obscure any effect of metformin on the endothelium. However, we did not see any differences in endothelium-independent vasodilatation, which we would expect to see if this was purely a vessel size effect or related to increased nitric oxide consumption.

Flow-mediated dilatation of the brachial artery is accepted as the gold standard for the non-invasive measurement of endothelial function as it is widely used, well tolerated, low risk and, importantly for our study population, suitable for use in pregnant women. There are, however, some limitations. Most notably for our study population, measurement of the vessel diameter can be technically challenging, particularly in the obese in whom visualisation of the intima is difficult as the ultrasound signal is attenuated by subcutaneous fat. Other limitations include the small sample size, the lack of longitudinal data for subjects other than those in the lean group and the variability of the baseline demographics (e.g. smoking status and parity) within the unblinded groups. This makes it difficult to identify differences within the small sample size.

In the larger EMPOWaR cohort as a whole, we saw no differences in blood pressure or the incidence of hypertensive disorders of pregnancy, which we may have expected if the placebo group had impaired endothelial function compared with the metformin group. This suggests that our finding of no difference between the two groups may be correct rather than a type 2 error. In conclusion, we have not demonstrated any effect on endothelial function of metformin in obese pregnant women.

Magnetic resonance imaging assessment of maternal and fetal adipose distribution

Introduction

For many years now it has been recognised that the site rather than the total quantity of body fat is an important determinant of insulin sensitivity and morbidity associated with obesity.[91–94] More recently, it has been recognised that deposition of lipid in 'ectopic' sites, namely the liver and skeletal muscle, is a major contributor to the development of insulin resistance.[95,96] It remains unclear whether or not increasing adiposity causes the deterioration in insulin sensitivity or vice versa. The 'portal hypothesis' of obesity suggests that an increase in central abdominal fat leads to elevated delivery of free fatty acids and inflammatory cytokines to the liver and that, consequently, hepatic insulin resistance develops and drives glucose upwards.[97] The 'spillover hypothesis' suggests that, in the context of obesity, the subcutaneous compartment becomes saturated and leads to the accumulation of visceral fat and deposition of lipid in ectopic sites such as the liver and muscle.[98] Clearly, the two hypotheses are not mutually exclusive and it is likely that both are contributory mechanisms. Regardless of the exact cause, there is no doubt that excess lipid accumulation is associated with impaired insulin sensitivity and morbidity such as type 2 diabetes mellitus.

Fat distribution in normal and obese pregnancy is less well studied and the contribution it pays to maternal and fetal outcomes and longer-term health is not clear. However, gestational weight gain is one of the most important predictors of post-partum weight retention[99] and thus contributes significantly to the obesity epidemic among young women.[100] Gestational weight gain is highly variable but in lean women the contribution from fat tends to be predominantly in the subcutaneous compartments, largely the trunk and thighs.[101,102] Obese women actually tend to gain less weight than lean women during pregnancy but the fat mass that they do gain tends to be more central and therefore potentially more metabolically harmful.[103]

Gestational weight gain and pre-existing obesity also impact on fetal growth. The conventional strategy for measurement of fetal growth is typically by ultrasound. Estimation of fetal weight is based on measurement of the fetal head circumference, femur length and abdominal circumference, with the abdominal circumference being the most individually sensitive predictor of fetal macrosomia.[104,105] The abdominal circumference is predominantly affected by the size of the fetal liver and is positively correlated with hepatic glycogen stores, which increase towards term.[106,107]

Glucose is the major substrate that determines fat accumulation in the fetus, with the greater the glucose supply the greater the deposition of fat.[108] There is a linear association between maternal glucose tolerance and neonatal adiposity at birth,[109] and a strong positive correlation between degree of maternal insulin resistance and neonatal fat mass at birth.[10] Increasing maternal BMI has also been shown to be associated with increased intrahepatocellular lipid in the newborn, assessed by magnetic resonance proton spectroscopy.[110]

Magnetic resonance imaging has been used for many years in pregnant women with no apparent adverse effects on the mother or developing fetus.[111,112] It enables the quantification of the different maternal fat depots, in contrast to other techniques that can measure only total body fat mass (e.g. ADP; see *Maternal and neonatal body composition*). This substudy also provided the opportunity to develop scanning protocols to assess the body composition of the fetus in utero.

The aim of this mechanistic substudy was to examine the effect of metformin on maternal and fetal fat deposition in the early and late third trimester. We hypothesised that improving insulin sensitivity with metformin would result in less deposition of fat in the more insulin-sensitive sites (i.e. visceral, hepatic and skeletal muscle) and potentially protect the fetus from accumulation of excess fat.

Methods

Participants in the EMPOWaR study were invited to undergo a MRI scan at 28 and 36 weeks' gestation. We aimed to recruit 40 participants to have a scan at both time points. Whole-body MRI and ^{1}H-MRS studies were performed on a Siemens MAGNETOM® Verio 3 Tesla MRI system (Siemens AG, Healthcare Sector, Erlangen, Germany). Participants were positioned in the magnet in a full left lateral position to avoid aortocaval compression. Data from the abdomen and thigh were acquired using a combination of spine and body matrix coils elements. Aural protection was provided by use of earplugs and headphones. Contact between the participant and scanning staff was maintained at all times. Heart rate and oxygen saturation were monitored continuously throughout the scan period; blood pressure was measured at the start of the scan and every 10 minutes throughout the procedure.

Scan sequences

Standard localising images were acquired to confirm organ and fetal position.

^{1}H-magnetic resonance spectroscopy

For ^{1}H-MRS measurement of intramyocellular and intrahepatocellular lipid, single-voxel spectra localised to the right quadriceps muscle and the right lobe of the liver were acquired using a point-resolved spectroscopy sequence (repetition time 5000 milliseconds/echo time 30 milliseconds) with and without water suppression and with eight signal averages. The voxel size was 2 cm^3 in the muscle and 3 cm^3 in the liver. The voxel site was chosen to avoid large blood vessels or subcutaneous adipose tissue. Lipid concentration was calculated from the water-suppressed acquisition using the spectroscopy analysis tool jMRUI (MRUI Consortium, Brno, Czech Republic).

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In- and out-of-phase imaging (Dixon method)

In addition to MRS, the Dixon method[113–115] was used for calculation of hepatic and skeletal muscle fat fraction in the participant and also fetal hepatic fraction. The lipid signal was calculated by subtraction of in- and out-of-phase images (2.46 milliseconds and 8.61 milliseconds) and T2* decay during this time, corrected using the two in-phase images (2.46 milliseconds and 4.92 milliseconds) according to protocols that are well established for use in the adult liver.[113–115] These protocols are not well established in fetal imaging and method development was required during the study to optimise this technique for the fetal measurements.

Assessment of maternal abdominal adipose tissue

To quantify maternal subcutaneous and visceral fat, a three-dimensional T1-weighted volumetric interpolated breath-hold examination sequence was acquired axially through the liver. Lipid signals were defined using a semiquantitative thresholding technique using the commercial software SliceOmatic™ (TomoVision, Magog, QC, Canada).

Adipose tissue appears bright on T1-weighted images. Regions of interest with attenuation above an investigator-defined threshold were coloured to define visceral adipose tissue and subcutaneous adipose tissue (*Figure 12*). The areas of the coloured regions were extracted, converted into a unit of volume (mm^3) and expressed as a percentage of the total abdominal volume of the region being examined. Volumes were calculated using the extracted areas of the regions of interest (mm^2) multiplied by the width of each slice (2 mm).

A multislice approach was used. The left renal pelvis was identified in all subjects and adipose tissue was measured in 20 2-mm slices cranial to this level.

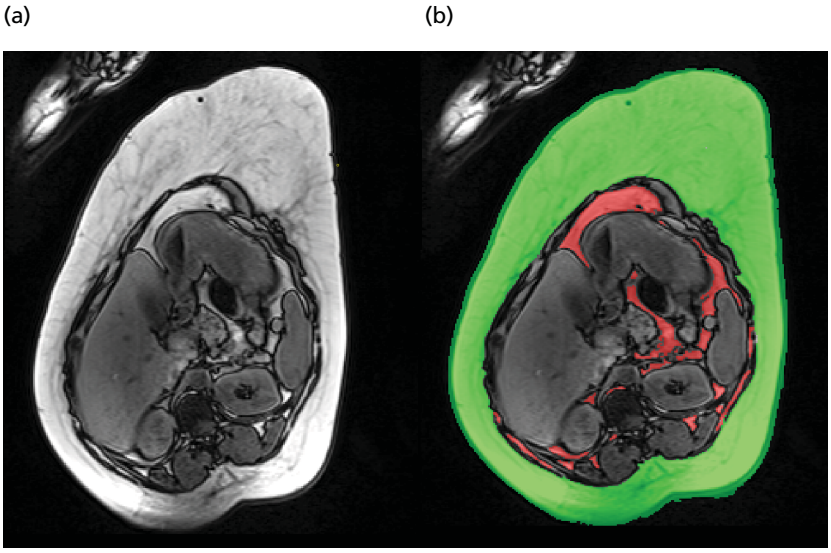


FIGURE 12 Maternal adipose tissue images. (a) Uncoloured and (b) coloured axial slices to show subcutaneous (green) and visceral (red) fat distribution.

Estimation of fetal liver volume

A T2 half-Fourier acquisition single-shot turbo spin-echo sequence was acquired of the fetus to cover the fetal liver in the axial, sagittal and coronal planes (dependent on degree of fetal movement during the acquisition period).

The fetal liver is identifiable by the investigator on these images using standard anatomical landmarks. The entire liver was coloured as the area of interest on every slice in which it was visible using the same software as was used for the maternal fat measurements (*Figure 13*). The area of the coloured region was extracted and converted into a unit of volume (mm^3) by multiplying the area (mm^2) by the width of each slice (2 mm).

Estimation of fetal hepatic fat and fetal subcutaneous fat

A T1-weighted fast low-angle shot (FLASH) sequence was acquired for the in- and out-of-phase fetal liver fat fraction. The slice thickness was 8 mm. For fetal subcutaneous fat, a fat excitation FLASH sequence was used, again with an 8-mm slice width. Shoulder-to-shoulder coverage of the fetus was obtained in the sagittal plane and a single slice at the level of the umbilical cord insertion was used in the axial plane. The subcutaneous fat was coloured on every available slice in the sagittal plane (*Figure 14*) and on the single slice in the axial plane using the same technique as described for the maternal subcutaneous and visceral fat and fetal liver volume. The amount of fat was expressed as a percentage of the total volume of the area examined. These protocols were subject to method development during the study process.

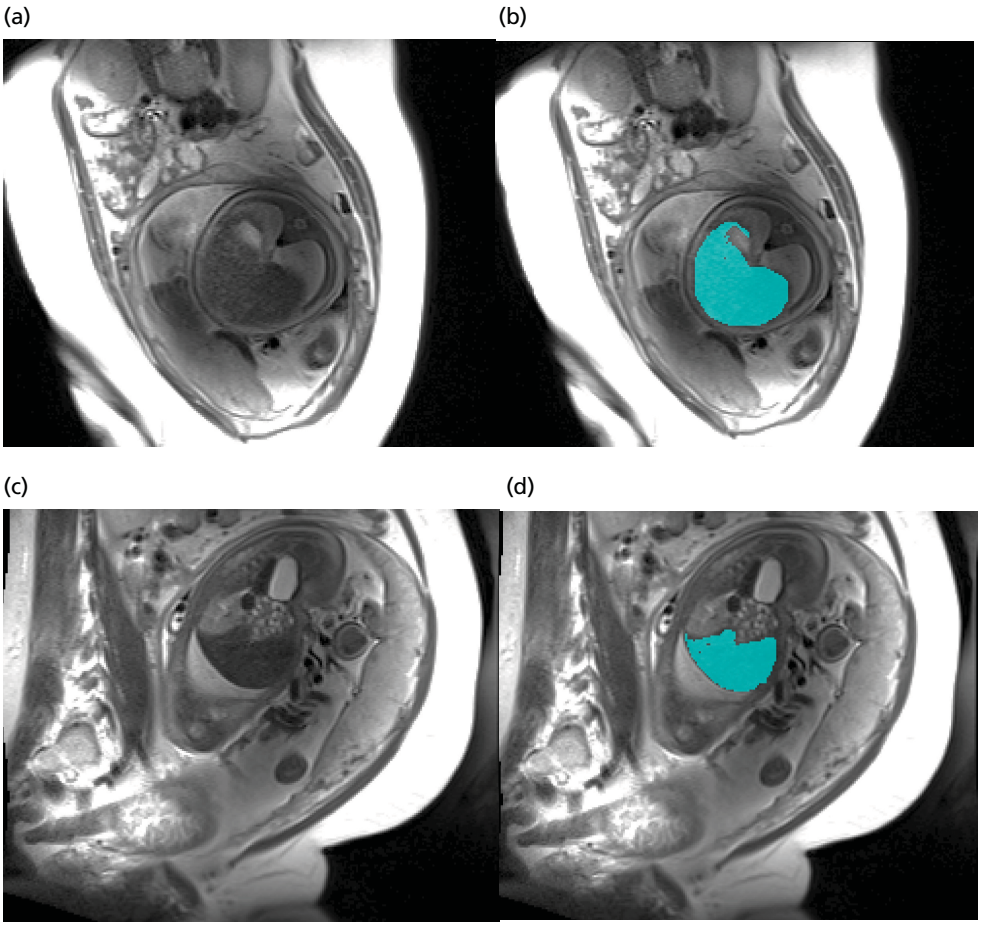


FIGURE 13 Fetal liver images. Uncoloured (a and c) and coloured (b and d) axial (a and b) and sagittal (c and d) slices to show the fetal liver.

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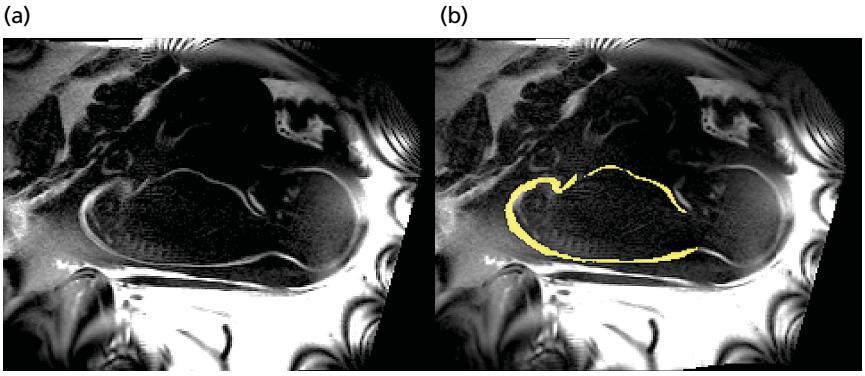


FIGURE 14 Fetal subcutaneous fat images. (a) Uncoloured and (b) coloured sagittal slices through the fetus to show the subcutaneous fat.

Statistical analysis

Comparisons between groups were made using unpaired *t*-tests or Mann–Whitney tests when data were not normally distributed. Comparisons within groups were made using paired *t*-test or Wilcoxon tests when data were not normally distributed. The Kruskal–Wallis test was used to compare differences between the groups over the two time points. Significance was set at $p < 0.05$.

Reproducibility

The intra- and interobserver variability for measurement of maternal abdominal adipose tissue using the same method as in this study has previously been validated and been found to be highly correlated.[116] Intraobserver variability for measurements of fetal liver volume and fetal subcutaneous fat was assessed by the same observer (CC) defining the region of interest on all relevant slices from five subjects on two separate occasions. Interobserver variability was assessed by comparison of data from all relevant slices for five subjects for two independent observers (CC and SS).

For each paired data set, a correlative plot of the data sets around the line of equality is presented. Agreement was assessed by construction of Bland–Altman plots with 95% limits of agreement as follows: upper 95% limit of agreement = mean difference + 2 SDs; lower 95% limit of agreement = mean difference – 2 SDs.

Results

The demographic characteristics of the participants are provided in *Table 13*. In total, 37 participants ($n = 18$ and $n = 19$ in the placebo and metformin groups, respectively) underwent MRI and ^{1}H-MRS studies at both 28 and 36 weeks' gestation. A further 10 participants ($n = 6$ and $n = 4$ in the placebo and metformin groups, respectively) underwent MRI at 28 weeks' gestation only and 10 participants ($n = 6$ and $n = 4$ in the placebo and metformin groups, respectively) underwent MRI at 36 weeks' gestation only.

Reproducibility

Fetal liver volume

Following repeated measurements by the same investigator (M1 and M2; intrarater) and of the same images by two investigators (CC and SS; inter-rater), measurements of fetal liver volume were found to be well correlated in both the sagittal (*Figures 15–18*) and axial (*Figures 19–22*) planes, with the majority of points scattered evenly around the line of no difference and within the upper and lower 95% limits of agreement. Measurement in the axial plane showed the best reproducibility. This may be because there is less rotation of the fetus on this axis and more reliable images were obtained.

TABLE 13 Characterisics of participants in the MRI substudy

Characteristic	Placebo ($n = 30$)	Metformin ($n = 27$)
Maternal		
Age (years), mean (SD)	29.4 (4.5)	30.1 (5.5)
Nulliparity, *n* (%)	11 (36.7)	11 (40.7)
BMI at baseline (kg/m^2), mean (SD)	38.2 (5.6)	39.4 (4.7)
Neonatal		
Male sex, *n* (%)	14 (46.7)	11 (40.7)
Birthweight (g), mean (SD)	3493.0 (512.4)	3596.1 (494.7)
Birthweight centile, mean (SD)	51.7 (29.6)	63.4 (25.8)
Ponderal index at birth, mean (SD)	3.44 (4.6)	2.60 (0.32)
Fat (%), mean (SD)	12.53 (5.7)	12.63 (4.3)
Tricep skinfold at birth (mm), mean (SD)	11.38 (18.1)	8.30 (2.5)
Subscapular skinfold at birth (mm), mean (SD)	10.06 (13.9)	7.11 (2.3)

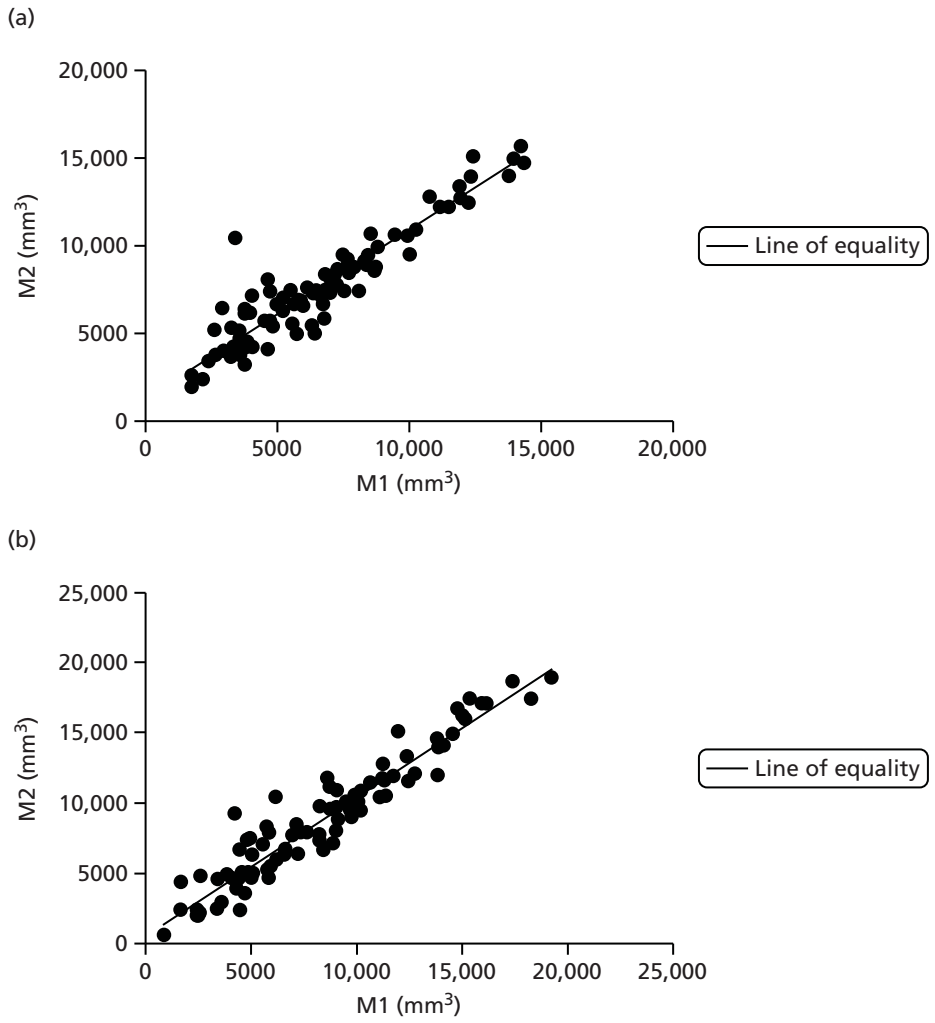


FIGURE 15 Sagittal fetal liver volume intrarater reproducibility. (a) Observer 1; and (b) observer 2. M1, measurement 1; M2, measurement 2, in reference to repeated measures by the same observer.

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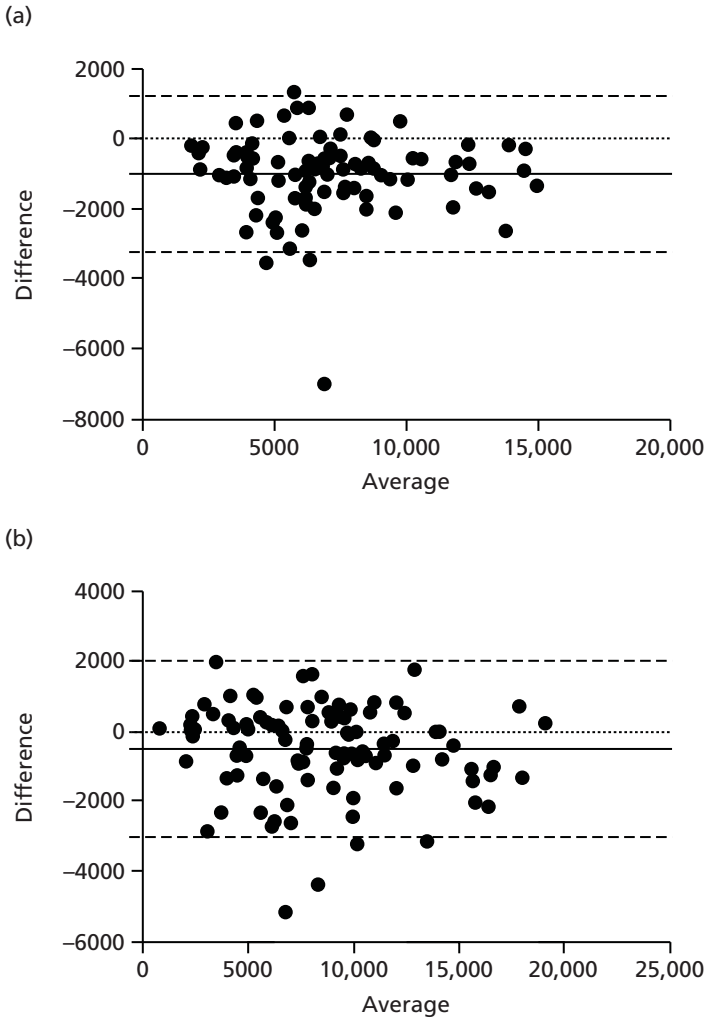


FIGURE 16 Sagittal fetal liver volume intrarater reproducibility: Bland–Altman analysis. (a) Observer 1. $n = 93$ pairs, mean difference (lower to upper 95% limits of agreement) –1015 (–3228 to 1198) mm^3; and (b) observer 2. $n = 99$ pairs, mean difference (lower to upper 95% limits of agreement) –495 (–3003 to 2014) mm^3.

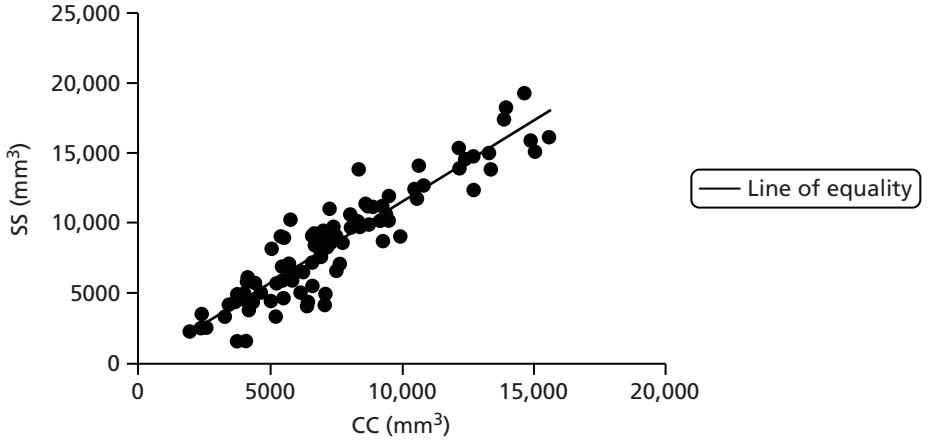


FIGURE 17 Sagittal fetal liver volume inter-rater reproducibility. CC, observer 1; SS, observer 2.

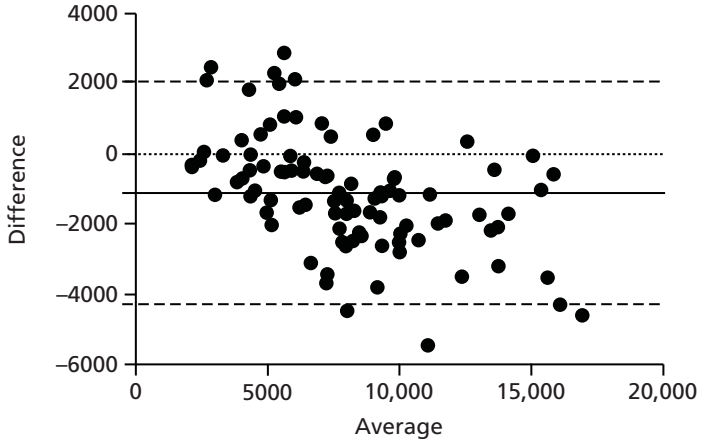


FIGURE 18 Sagittal fetal liver volume inter-rater reproducibility: Bland–Altman analysis. $n = 96$ pairs, mean difference (lower to upper 95% limits of agreement) –1110 (4284 to 2065) mm^3.

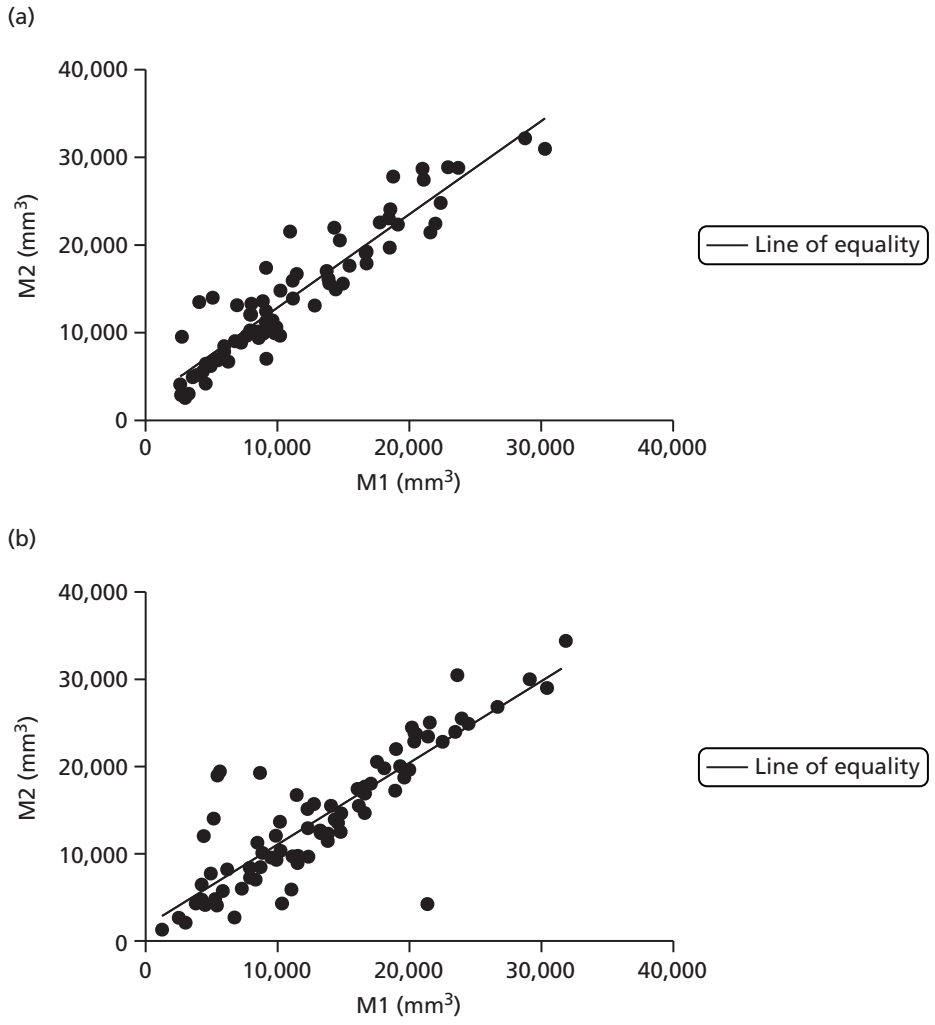


FIGURE 19 Axial fetal liver volume intrarater reproducibility. (a) Observer 1; and (b) observer 2. M1, measurement 1; M2 measurement 2, in reference to repeated measures by the same observer.

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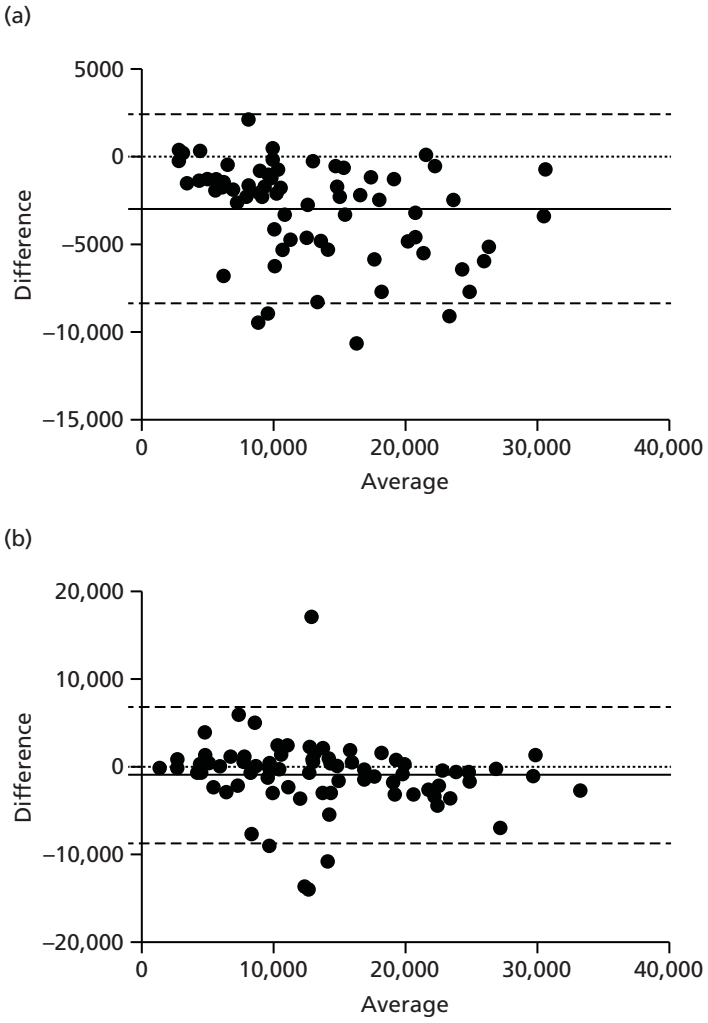


FIGURE 20 Axial fetal liver volume intrarater reproducibility: Bland–Altman analysis. (a) Oberver 1: $n = 71$ pairs, mean difference (lower to upper 95% limits of agreement) –2965 (–8335 to 2404) mm^3; and (b) observer 2: $n = 80$ pairs, mean difference (lower to upper 95% limits of agreement) –853 (–8575 to 6869) mm^3.

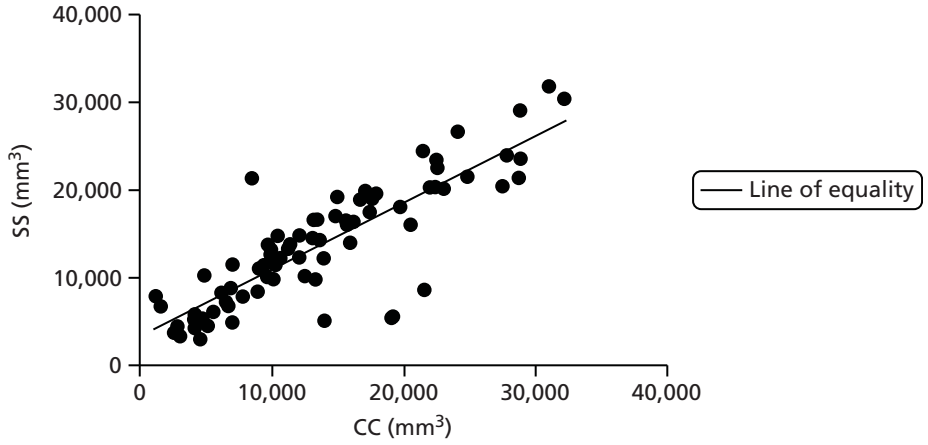


FIGURE 21 Axial fetal liver volume inter-rater reproducibility. CC, observer 1; SS, observer 2: $n = 93$ pairs, mean difference (lower to upper 95% limits of agreement) –1015 (–3228 to 1198) mm^3.

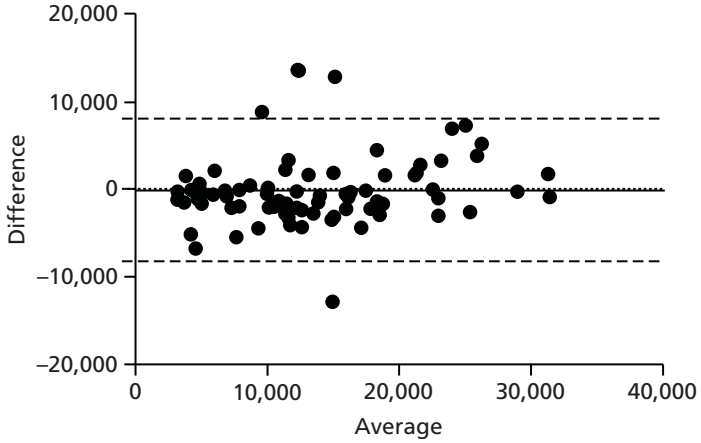


FIGURE 22 Axial fetal liver volume inter-rater reproducibility: Bland Altman analysis. $n = 77$ pairs, mean difference (lower-upper 95% limits of agreement) –92.84 (–8255 to 8069) mm^3.

Fetal subcutaneous fat, intrarater variability

Repeated measures by the same investigator were performed. Repeated measures for this parameter were less highly correlated, as demonstrated by a wider scatter of points around the line of equality (*Figure 23*) and between the 95% limits of agreement (*Figure 24*). This is likely to reflect both the smaller number of suitable images for analysis of fetal subcutaneous fat and the fact that this was a novel technique that required significant method development during the study period.

Maternal subcutaneous and visceral fat masses

There was no difference in the subcutaneous fat mass (expressed as a percentage of the abdominal volume examined) between the placebo group and the metformin group at 28 weeks' gestation (difference between means –3.45%, 95% CI –7.63% to 0.73%; $p = 0.10$) or at 36 weeks' gestation (difference between means –3.43%, 95% CI –7.63% to 0.76%; $p = 0.11$). There was no difference in visceral fat mass (expressed as a percentage of the abdominal volume examined) at 28 weeks' gestation (difference between means –0.02%, 95% CI –1.93% to 1.89%; $p = 0.98$) or at 36 weeks' gestation (difference between means 0.18%, 95% CI –2.17% to 1.82%; $p = 0.86$) (*Figure 25*).

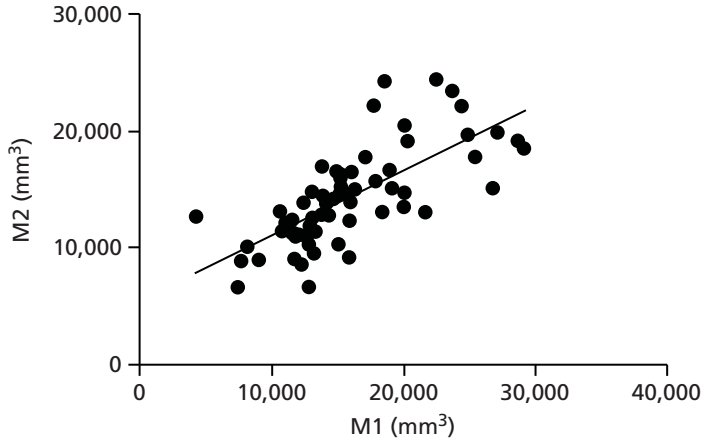


FIGURE 23 Fetal subcutaneous fat intrarater reproducibility. M1, measurement 1; M2, measurement 2, in reference to repeated measures by the same observer.

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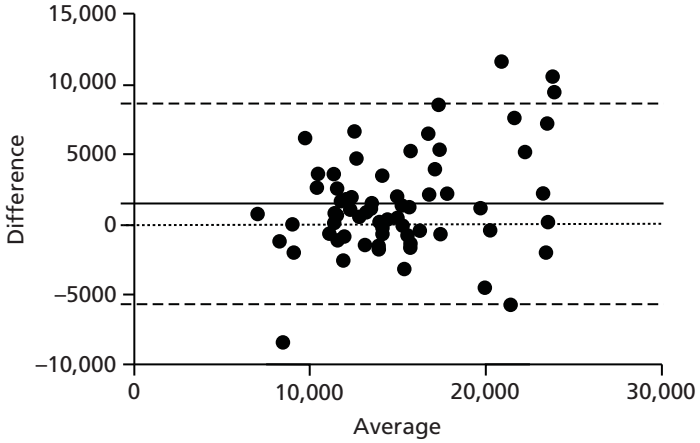


FIGURE 24 Fetal subcutaneous fat intrarater reproducibility: Bland–Altman analysis. $n = 67$ pairs, mean difference (lower to upper 95% limits of agreement) 1530 (–5630 to 8691) mm^3.

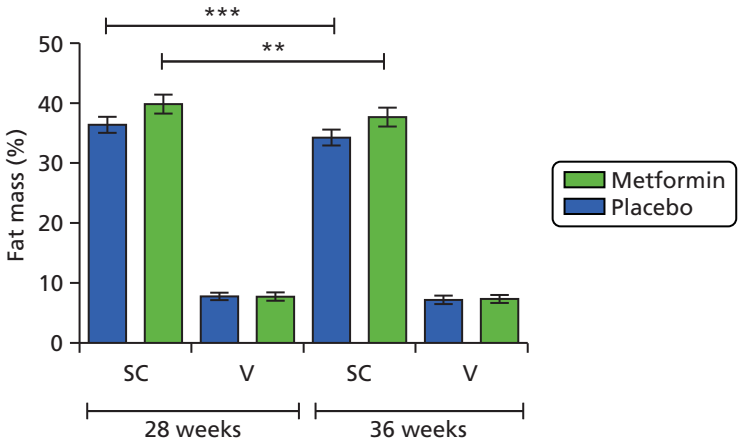


FIGURE 25 Maternal subcutaneous (SC) and visceral (V) fat mass at 28 and 36 weeks' gestation. $^{**}p \leq 0.01$, $^{***}p \leq 0.001$.

Both groups demonstrated a significant loss of subcutaneous fat mass between 28 and 36 weeks' gestation (paired *t*-test: placebo difference between means –2.14, 95% CI –3.27% to –1.01%; $p = 0.0009$; metformin difference between means –2.15, 95% CI –3.38% to –0.923%; $p = 0.0018$). There was no significant difference in the percentage change in subcutaneous fat mass from 28 to 36 weeks' gestation between the placebo group and the metformin group (difference between means –0.45, 95% CI –4.71% to 3.82%; $p = 0.83$) (*Figure 26*).

Neither group demonstrated any change in visceral fat mass between 28 and 36 weeks' gestation and thus there was no difference in change in visceral fat mass between 28 and 36 weeks' gestation between the groups (Mann–Whitney test, $p = 0.60$) (see *Figure 26*).

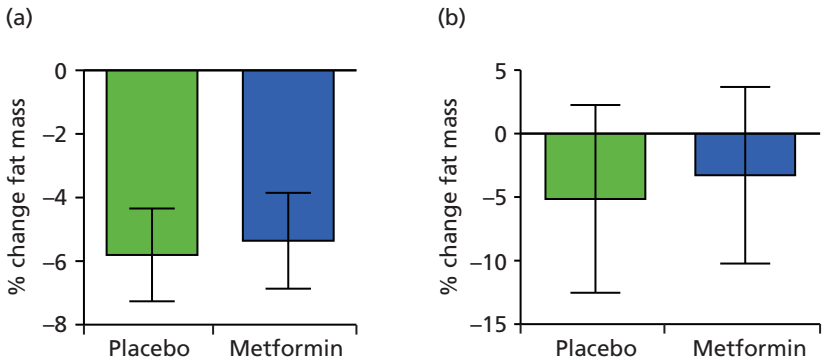


FIGURE 26 Percentage change in (a) subcutaneous and (b) visceral fat mass between 28 and 36 weeks' gestation.

Maternal skeletal muscle and hepatic fat fraction

Dixon method

The mean (SD) hepatic fat fraction (%) at 28 weeks' gestation was 3.93 (1.35) and 4.90 (2.76) in the placebo and metformin groups, respectively. At 36 weeks' gestation the equivalent figures were 5.16 (2.78) and 5.00 (2.54).

The mean (SD) skeletal muscle fat fraction (%) at 28 weeks' gestation was 2.84 (0.90) and 3.20 (1.33) in the placebo and metformin groups, respectively. At 36 weeks' gestation the equivalent figures were 3.43 (1.29) and 3.62 (1.82).

There were no significant differences in fat fraction measured by the Dixon method by gestation or treatment group in either the skeletal muscle ($p = 0.55$) or the liver ($p = 0.50$) (*Figure 27*).

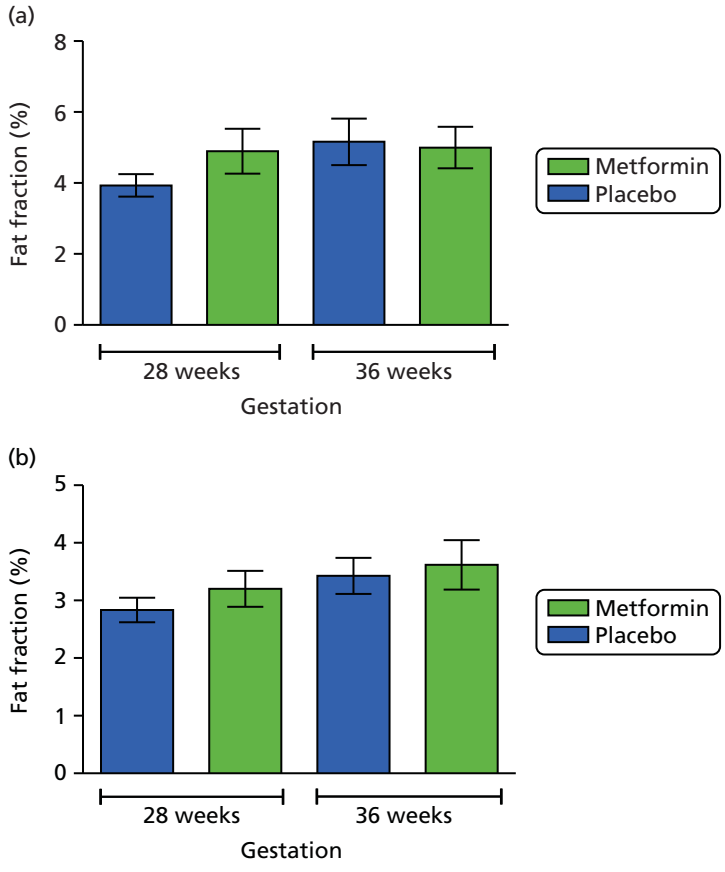


FIGURE 27 Maternal (a) hepatic and (b) skeletal muscle fat fraction measured by the Dixon method.

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^{1}H-magnetic resonance spectroscopy method

The mean (SD) hepatic fat fraction (%) at 28 weeks' gestation was 1.24 (1.26) and 0.87 (1.22) in the placebo and metformin groups, respectively. At 36 weeks' gestation the equivalent figures were 1.11 (1.80) and 0.86 (0.71).

The mean (SD) skeletal muscle fat fraction (%) at 28 weeks' gestation was 7.13 (3.77) and 7.55 (4.86) in the placebo and metformin groups, respectively. At 36 weeks' gestation the equivalent figures were 10.99 (9.60) and 9.10 (4.46).

There were no significant differences in fat fraction measured by ^{1}H-MRS by gestation or treatment group in either the skeletal muscle ($p = 0.64$) or the liver ($p = 0.42$) (*Figure 28*).

Fetal liver volume, hepatic fat fraction and subcutaneous fat

There was no statistically significant difference in fetal liver volume at 28 or 36 weeks' gestation between the placebo group and the metformin group. Both groups demonstrated a significant increase in liver volume over time ($p < 0.0001$), as would be expected, but the percentage increase was not significantly different between the two groups when measured in either plane (*Figures 29* and *30*). There was no change in the fetal hepatic fat fraction by gestation or treatment group (*Figure 31*). There was no difference in subcutaneous fat, measured in the sagittal and axial planes (expressed as a percentage of body volume), at 36 weeks' gestation between the two treatment groups (*Figure 32*).

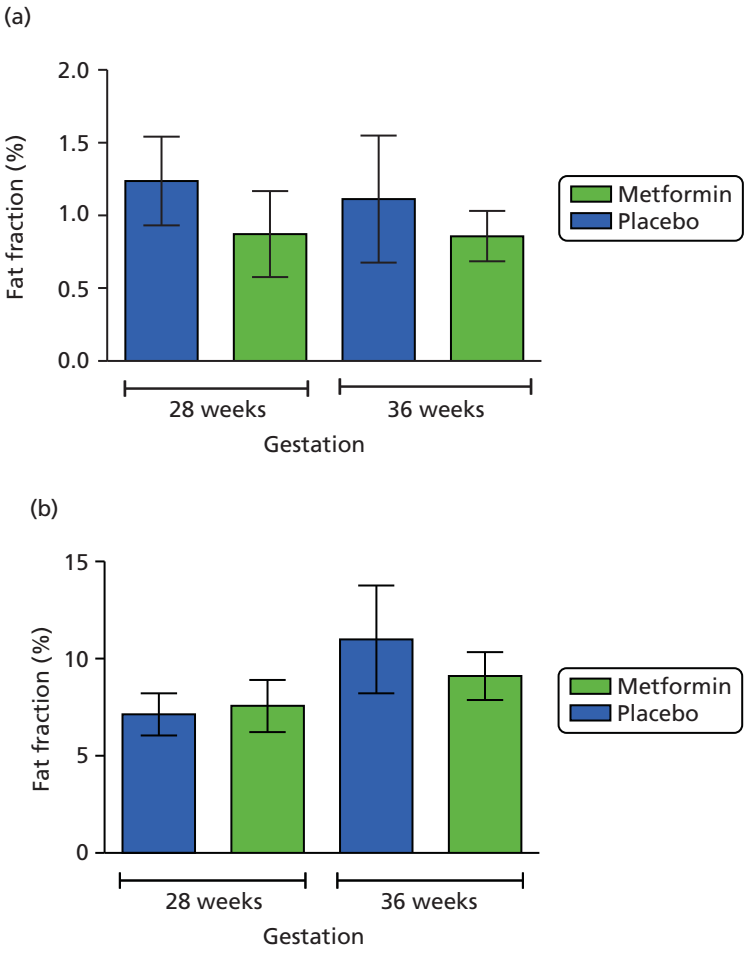


FIGURE 28 Maternal (a) hepatic and (b) skeletal muscle fat fraction measured by ^{1}H-MRS.

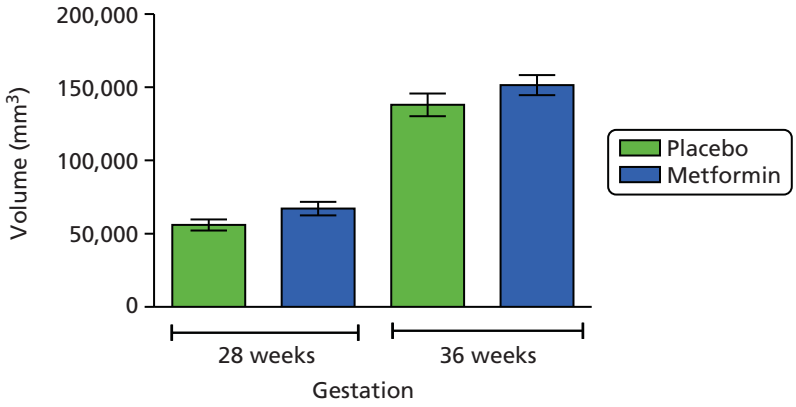


FIGURE 29 Fetal liver volume: axial plane. Placebo: 28 weeks, $n = 25$; 36 weeks, $n = 22$; metformin: 28 weeks, $n = 22$; 36 weeks, $n = 22$.

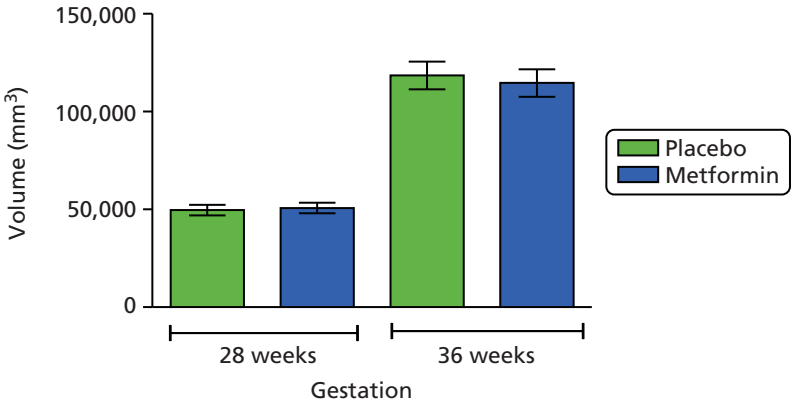


FIGURE 30 Fetal liver volume: sagittal plane. Placebo: 28 weeks, $n = 25$; 36 weeks, $n = 23$; metformin: 28 weeks, $n = 23$; 36 weeks, $n = 22$.

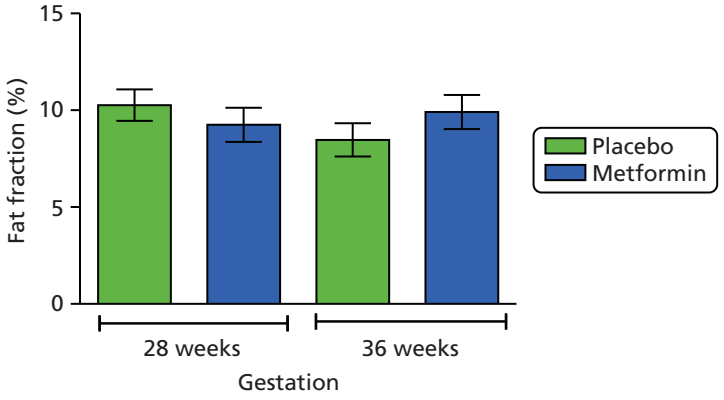


FIGURE 31 Fetal hepatic fat fraction. Placebo, $n = 17$; metformin, $n = 16$ (paired samples).

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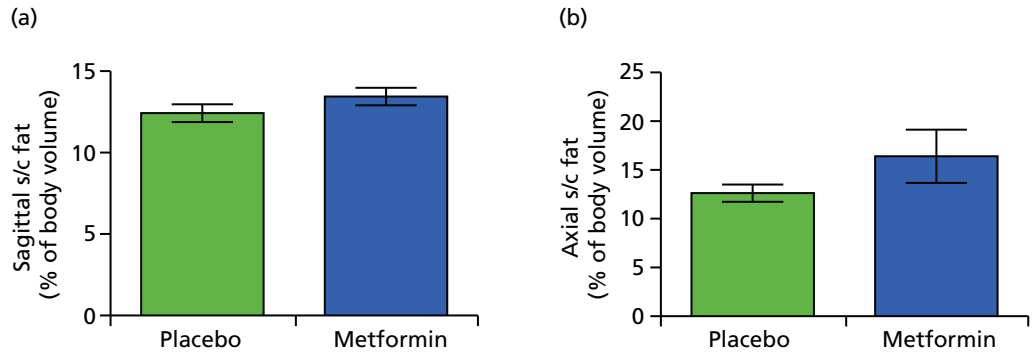


FIGURE 32 Fetal subcutaneous (s/c) fat volume: (a) sagittal plane; and (b) axial plane. Subcutaneous fat sagittal plane: placebo, $n = 14$; metformin, $n = 25$; subcutaneous fat axial plane: placebo, $n = 8$; metformin, $n = 5$.

Discussion

The purpose of this substudy was to assess whether or not distribution of body fat in obese pregnant women was altered by metformin. We also examined the fetus with the aim of assessing effect on liver volume, hepatic fat content and fetal subcutaneous fat deposits. We aimed to scan 40 participants at both 28 and 36 weeks' gestation. Ultimately, we scanned 57 participants, with longitudinal maternal data available for 37 participants (those who attended for both scans). We obtained longitudinal fetal hepatic lipid data in 17 and 16 of the participants allocated to the placebo and metformin groups, respectively. Liver volume was successfully measured in the axial plane in 25 and 22 fetuses at 28 and 36 weeks, respectively, in participants allocated to placebo and in 22 fetuses at both time points in participants allocated to metformin. Liver volume was successfully measured in the sagittal plane in 25 and 23 fetuses at 28 and 36 weeks, respectively, in participants allocated to placebo and in 22 fetuses at both time points in participants allocated to metformin. Subcutaneous fat mass was measured in the sagittal plane in 14 and 25 subjects allocated to placebo and metformin, respectively. In the axial plane it was successfully measured in eight and five subjects in the placebo and metformin groups, respectively.

We have demonstrated that the maternal scanning protocols work well in obese pregnant women, with good inter- and intrarater correlation. We have shown that it is possible to obtain the fetal data as we had planned, although not in every subject scanned because of fetal movement and time limitations, with priority being given to acquisition of the maternal data. There was reasonably good inter- and intrarater correlation for the fetal liver volume data. Correlation was less good for the subcutaneous fat measurements but the cohort numbers were small for this study.

In summary, participants in both the placebo and the metformin arms of the study lost subcutaneous fat over the course of pregnancy but there was no difference in the percentage change between the two groups. We saw no differences in the amounts of visceral fat either between treatment groups or by gestation. Ectopic lipid deposition in both the liver and skeletal muscle was also the same in both groups and did not change between 28 and 36 weeks' gestation.

Mean hepatic fat fraction in both groups was relatively low, particularly when measured by ^{1}H-MRS. When measured using the Dixon method, it was higher than we have previously seen in a cohort of 10 lean and 10 obese non-diabetic pregnant women[116] but still lower than in a cohort of obese non-pregnant women[117] and certainly below the diagnostic threshold for non-alcoholic fatty liver disease.[118] Mean skeletal muscle fat fraction measured by ^{1}H-MRS was similar to that in our previous cohort of obese pregnant women[116] and to that of a group of normally glucose-tolerant obese (mean BMI 30 kg/m^2) non-pregnant women.[119] This suggests that pregnancy itself, rather than metformin, may be exerting a protective effect on the liver, which deters accumulation of lipid in this site.

The fetal data must be interpreted with a greater degree of caution. The scanning protocols are not well established and were subject to some method development during the study period. Fetal movement during the image acquisition period is an extra challenge. We aimed to limit the scan duration to 60 minutes, which was the limit of acceptability for the participants, and we prioritised the acquisition of maternal data in this time. However, we still acquired a reasonable amount of data suitable for analysis and have not demonstrated any differences in fetal liver volumes or hepatic and subcutaneous fat depots between the placebo group and the metformin group. This is in keeping with the primary outcome of the EMPOWaR trial, which demonstrated no difference in birthweight of the babies, and also the secondary outcomes, for which we saw no difference in neonatal fat mass measured by ADP or in neonatal skinfold thicknesses (see *Maternal and neonatal body composition*).

In conclusion, we have not demonstrated any effect of metformin in obese pregnant women on maternal or fetal body fat distribution at 28 and 36 weeks' gestation.

The effect of metformin on the hypothalamic–pituitary–adrenal axis

Background

It is now well recognised that the intrauterine environment is a key time for determining not only fetal growth and consequent birthweight but also future life health, a concept known as 'early life programming'.[120] One of the key mechanisms thought to be responsible for programming is overexposure of the fetus to glucocorticoids, with consequent alterations to the fetal hypothalamic–pituitary–adrenal (HPA) axis.[121,122]

The maternal HPA axis undergoes significant activation during pregnancy, resulting in a substantial increase in maternal cortisol levels.[123,124] This is partly because of placental secretion of large quantities of corticotrophin-releasing hormone.[125] These physiological changes in the HPA axis are essential for normal fetal growth and development and promotion of fetal organ maturation and are also thought to have a role in a gestational clock mechanism signalling the appropriate time for the onset of labour.[126] However, over- and possibly underexposure to glucocorticoids in utero can have adverse effects on the fetus that persist into adult life. Glucocorticoids are lipophilic and readily cross the placenta, yet fetal glucocorticoid levels are tenfold lower than maternal levels because of the action of placental 11β-HSD2.[127] 11β-HSD2 acts as a placental enzyme barrier that converts active cortisol into inactive cortisone,[127] thus protecting the fetus from overexposure to excess glucocorticoid. Both animal and human studies have suggested that the efficiency of placental 11β-HSD2 is variable and may be weakened by factors such as diet, infection, inflammation, hypoxia and stress,[121,122] thus allowing greater transplacental passage of cortisol to the fetus. Even modest changes in placental 11β-HSD activity appear to have the potential to significantly alter fetal exposure.[128,129]

Glucocorticoids exert their effect through the glucocorticoid receptor (GR), which acts as a transcription factor. The activated GR translocates to the nucleus, binds to GR response elements in the promoters of target genes and influences their transcription.[130] 11β-HSD1 is the enzyme that converts cortisone back to cortisol. Alterations in levels of GR could also affect the sensitivity of the placenta to cortisol and alterations in levels of 11β-HSD1 will affect cortisol availability.

The impact of undernutrition in pregnancy on the HPA axis has been extensively studied in both animal models and human cohorts. It is difficult to ascertain the impact of diet alone because of potential confounding from the impact of stress but it would appear that prenatal exposure to undernutrition has an adverse impact on long-term health, mediated in part through overexposure to intrauterine glucocorticoid.[131] The impact of overnutrition or obesity in pregnancy on the HPA axis is not yet known. In the non-pregnant population, obesity is associated with activation of the HPA axis but there is associated increased hepatic metabolism and renal excretion of cortisol results in near-normal levels of circulating cortisol.[132–134] If dysregulation is maintained during pregnancy, fetuses of obese women may be

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exposed to altered levels of glucocorticoids compared with fetuses of lean women, with consequent impact on birthweight and health in later life. The current data on the impact of obesity are conflicting. One study found that women who were obese at the start of pregnancy had elevated evening salivary cortisol in the third trimester, particularly women who had gestational weight gain greater than that in Institute of Medicine guidelines.[135] Another study demonstrated higher hair cortisol (a measure of longer-term cortisol exposure) in obese women.[136] Contrary to this, our own recently published data suggest that obese women have lower total serum levels of cortisol and lower calculated free levels of cortisol through pregnancy than lean women,[137] suggesting that cortisol exposure to the fetus may be lower in obese pregnancy. A better understanding of the impact of obesity on offspring birthweight and the maternal and fetal HPA axis is clearly required.

As the primary outcome of our study was birthweight, and fetal exposure to cortisol is a likely determinant of birthweight, this mechanistic substudy was designed to examine the effect of metformin on maternal salivary cortisol levels (as a measure of cortisol exposure). Furthermore, as placental glucocorticoid metabolism is known to be tightly regulated by changes in inflammation, and in a rodent model metformin altered expression of genes involved in glucocorticoid metabolism in skeletal muscle and adipose tissue, we tested whether or not treatment with metformin had any effect on the placental expression of genes regulating fetal glucocorticoid exposure, including GR, 11β-HSD1 and 11β-HSD2.

Methods

Salivary cortisol

For the measurement of diurnal cortisol patterns, all participants in the study were invited to submit bedtime and waking saliva samples at the baseline visit (after randomisation but before starting study treatment) and at 28 and 36 weeks' gestation. Saliva samples were collected in Salivette® (Sarstedt, Nümbrecht, Germany) containers at bedtime and on waking, and time of collection was recorded on the containers. Participants were asked not to eat, drink, smoke or brush their teeth for the half-hour preceding collection. Participants were asked to store the samples in their home refrigerator for no more than 1 week and post them back to our laboratory. Samples were then stored at –80 °C.

Salivary cortisol was measured by ELISA using a standard kit from Demeditec Diagnostics (Kiel, Germany) according to the manufacturer's protocol. The limit of detection was 2.5 ng/ml, with a mean intra-assay CV of 5.6% and a mean interassay CV of 6.9%.

Statistical analysis

Data were compared between treatment groups using a linear regression model, adjusted by BMI band (30–39 kg/m^2 vs. > 40 kg/m^2). Data were log-transformed for analysis and transformed back to natural numbers for presentation of the results.

Placental biopsies

A subset of women participating in the study consented to placental biopsy. The characteristics of participants in the substudy were similar to those of the women in the study overall. Samples were collected and the study carried out blind to treatment allocation.

Sample preparation

Placental biopsies were obtained at delivery from consenting women participating in the EMPOWaR trial in accordance with the SOP (see *Appendix 7*). Samples were stored in RNA Later® solution (ThermoFisher Scientific) for 24 hours at 4 °C. The RNA Later solution was then removed and the tissue stored at –80 °C prior to analysis.

Ribonucleic acid extraction and quantitative real-time reverse transcription polymerase chain reaction

Ribonucleic acid (RNA) was extracted from 40–60 mg of tissue using the RNeasy® Mini RNA extraction kit (Qiagen, Manchester, UK), according to the manufacturer's protocol. A deoxyribonuclease step was included to remove genomic deoxyribonucleic acid (DNA) from the samples. The RNA obtained was assessed for quality and quantity using the RNA 6000 Nano Kit and Bioanalyzer (Agilent Technologies, Stockport, UK), according to the manufacturer's protocol. Complementary deoxyribonucleic acid (cDNA) was synthesised from RNA (1 µg) using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems™, Life Technologies, Loughborough, UK) in a 50-µl reaction, according to the manufacturer's protocol. Negative controls [no RNA (water) and no reverse transcriptase (RT)] were included.

The expression of GR (*NR3C1*), 11β-HSD1 and 11β-HSD2 was quantified using Taqman® Gene Expression Assays: GR (Hs00353740_m1), HSD1 (Hs01547870_m1) and HSD2 (Hs00388669_m1), with tyrosine 3-mono-oxygenase/tryptophan 5-mono-oxygenase activation protein, zeta polypeptide (*YWHAZ*, Hs03044281_g1) used as an endogenous control (ThermoFisher, Renfrew, UK). All probes spanned exons so would not amplify any residual genomic DNA present. Samples were assayed in triplicate on 384-well plates. Samples from the same patient for the different gene expression assays were run on the same plate. Negative controls [no RNA, no RT, no cDNA (water)] were included on every plate. A cDNA sample from one patient (chosen as the sample had high levels of good-quality RNA) was included on every plate to show interplate variation and act as a calibrator sample. Plates were run on a 7900HT bioanalyser (Applied Biosystems, Foster City, CA, USA). Gene expression was calculated using the 2-ΔΔCt method of analysis.[138]

Statistical analysis

Gene expression data were compared between treatment groups using a linear regression model, adjusted by BMI band (30–39 kg/m^2 vs. > 40 kg/m^2) and mode of delivery (vaginal delivery vs. caesarean section) as these factors are known to affect gene expression in the placenta.[139] Data were log-transformed for analysis and transformed back to natural numbers for presentation of results.

Results

Salivary cortisol

Samples were obtained from 235 participants. Unblinding after data lock revealed final cohort numbers as detailed in *Table 14*. Baseline demographics were similar between the two groups and are also shown in *Table 14*.

There was no difference in the increment of mean cortisol on waking at each gestation time point between the placebo group and the metformin group (*Table 15* and *Figure 33*).

TABLE 14 Baseline characteristics of participants in the salivary cortisol substudy

	ITT		Per protocol	
Characteristic	Placebo ($n = 121$)	Metformin ($n = 114$)	Placebo ($n = 77$)	Metformin ($n = 79$)
Age (years), mean (SD)	29.9 (5.0)	29.1 (5.6)	29.8 (5.0)	29.9 (5.5)
Nulliparity, mean (SD)	50 (41.3)	52 (45.6)	30 (39.0)	38 (48.1)
BMI (kg/m^2), mean (SD)	36.9 (5.0)	37.5 (5.2)	36.7 (5.0)	37.2 (4.6)
Current smoking, *n* (%)	9 (7.4)	15 (13.2)	5 (6.5)	8 (10.1)
Highest educational qualification, *n* (%)				
Up to 16 years	41 (33.9)	31 (27.2)	23 (29.9)	16 (20.3)
> 16 years	80 (66.1)	83 (72.8)	54 (70.1)	63 (79.7)

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TABLE 15 Salivary cortisol (mmol/l)

	ITT							Per protocol						
	Placebo		Metformin		Adjusted mean difference	95% CI	*p*-value	Placebo		Metformin		Adjusted mean difference	95% CI	*p*-value
Time point	Mean	SD	Mean	SD				Mean	SD	Mean	SD			
Baseline														
n	107		101					70		72				
Bedtime	2.23	8.0	1.99	2.38				1.51	3.7	2.00	2.7			
Waking	9.03	24.6	6.4	3.9				10.23	30.2	6.42	3.5			
Mean difference	–6.80	22.5	–4.36	5.1	1.023	0.978 to 1.071	0.3111	–8.72	26.7	–4.42	5.0	1.040	0.973 to 1.111	0.2429
28 weeks														
n	48		52					36		47				
Bedtime	3.17	4.0	2.04	1.6				3.19	4.0	2.04	1.7			
Waking	8.68	6.9	9.26	4.3				9.28	7.7	9.26	4.5			
Mean difference	–5.51	7.8	–7.22	3.7	0.994	0.984 to 1.004	0.2223	–6.09	8.2	–7.22	3.9	0.997	0.987 to 1.008	0.6153
36 weeks														
n	36		41					28		35				
Bedtime	3.40	3.15	2.98	1.8				3.63	3.5	2.89	1.7			
Waking	8.90	4.2	8.74	4.8				8.99	4.3	9.04	5.1			
Mean difference	–5.50	3.7	–5.74	5.6	0.999	0.990 to 1.008	0.7780	–5.35	3.7	–6.15	5.9	0.996	0.986 to 1.007	0.4921

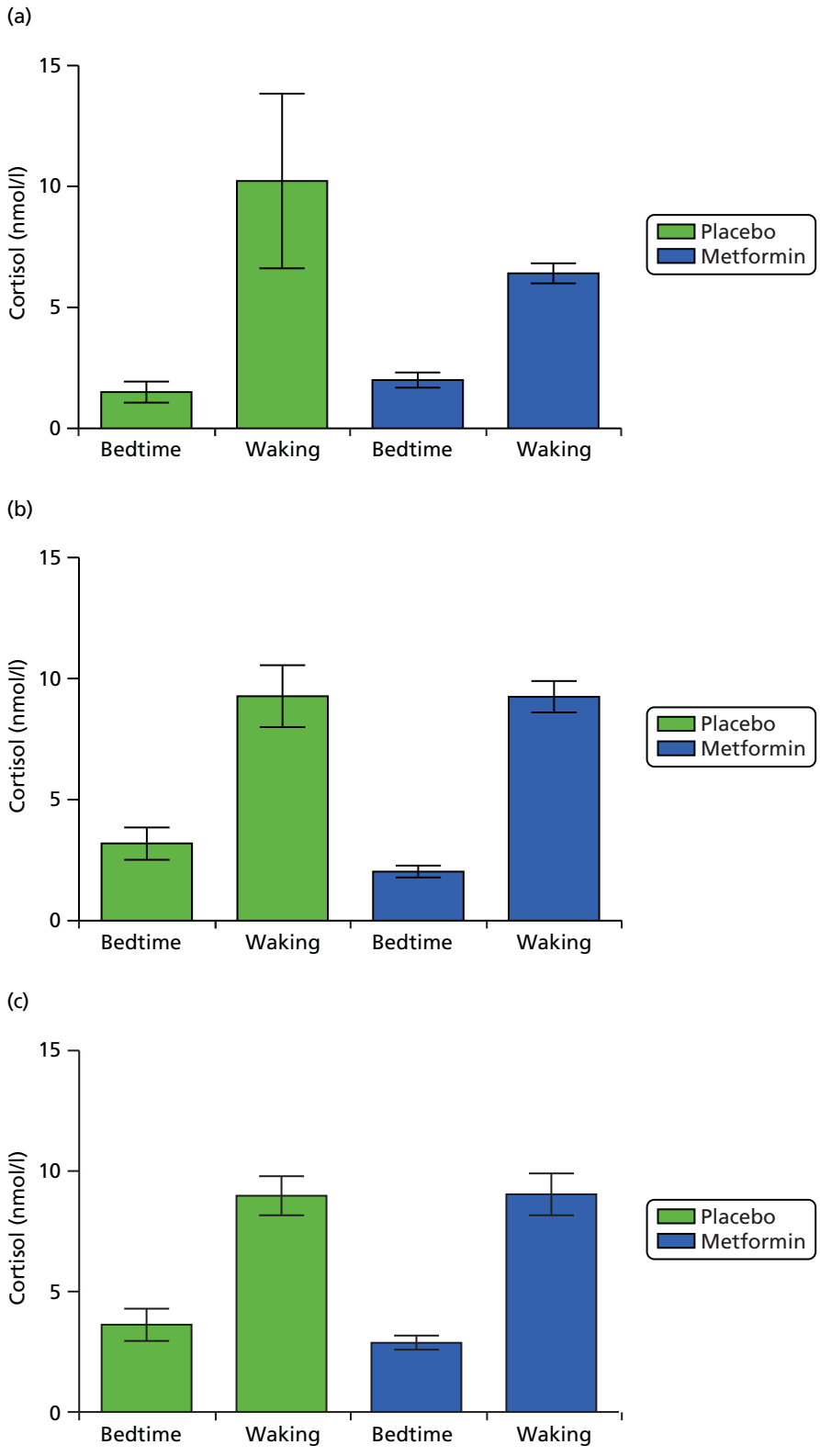


FIGURE 33 Bedtime and waking salivary cortisol: (a) baseline; (b) 28 weeks; and (c) 36 weeks.

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Placental biopsies

Samples were obtained from 125 participants from six participating centres. Unblinding after data lock revealed final cohort numbers as follows: placebo group $n = 64$ and metformin group $n = 61$ for ITT analysis; placebo group $n = 53$ and metformin group $n = 52$ for per-protocol analysis (as previously defined). Baseline demographics were similar between the two groups and are shown in *Table 16*.

There were differences in RNA quality but not RNA yield according to recruitment centre. However, all of the RNA samples were used for cDNA synthesis and all samples gave results for gene expression. There was no indication of any variation between plates. None of the negative controls showed contamination in the reverse transcription polymerase chain reaction process.

The gene expression results are shown in *Table 17*. There was no difference in GR, 11β-HSD1 or 11β-HSD2 mRNA levels (relative to control gene expression) between the two treatment groups after adjustment for mode of delivery and BMI band. This was the same for both the ITT analysis and the per-protocol analysis.

TABLE 16 Baseline characteristics of participants in the placental biopsy study

	ITT		Per protocol	
Characteristic	Placebo ($n = 64$)	Metformin ($n = 61$)	Placebo ($n = 53$)	Metformin ($n = 52$)
Age (years), mean (SD)	29.2 (5.5)	29.7 (5.3)	29.1 (5.4)	30.3 (5.3)
BMI (kg/m^2), mean (SD)	37.0 (5.2)	38.3 (5.3)	36.4 (4.7)	37.8 (4.8)
Current smoking, *n* (%)	7 (10.9)	10 (16.4)	5 (9.4)	7 (13.5)
Highest educational qualification, *n* (%)				
Up to 16 years	20 (31.3)	13 (21.3)	18 (34.0)	9 (17.3)
> 16 years	44 (68.8)	48 (78.7)	35 (66.0)	43 (82.7)
Mode of delivery, *n* (%)				
Vaginal	37 (57.8)	41 (67.2)	31 (58.5)	37 (71.2)
Caesarean section	27 (42.2)	20 (32.8)	22 (41.5)	15 (28.8)
Gestation at delivery (days), mean (SD)	277.5 (9.4)	277.6 (9.6)	277.3 (9.5)	277.8 (10.1)
Male baby sex, *n* (%)	31 (48.4)	34 (55.7)	24 (45.3)	28 (53.8)

TABLE 17 Gene expression results for placental biopsies

	ITT							Per protocol						
	Placebo		Metformin		Estimated mean difference			Placebo		Metformin		Estimated mean difference		
Gene expression	Mean	SD	Mean	SD		95% CI	*p*-value	Mean	SD	Mean	SD		95% CI	*p*-value
GR[a,b]	0.8404	0.49	0.8088	0.44	0.975	0.790 to 1.206	0.82	0.7963	0.41	0.8410	0.45	1.060	0.857 to 1.311	0.59
11β-HSD1[b,c]	2.2783	3.09	2.4612	3.20	1.142	0.725 to 1.802	0.56	2.2935	3.09	2.4747	3.38	1.117	0.666 to 1.876	0.67
11β-HSD2[b,c]	4.2637	7.28	3.3163	5.40	0.855	0.588 to 1.241	0.41	3.5363	5.50	3.6518	5.78	0.970	0.662 to 1.423	0.88

a mRNA levels expressed relative to control gene *NR3C1*.
b Data were log-transformed for statistical analysis and transformed back to natural numbers for this table.
c mRNA levels expressed relative to control gene *YWHAZ*.

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Discussion

We have not demonstrated any differences in bedtime or waking salivary cortisol between obese women taking metformin and those taking placebo. The findings should be interpreted with caution as the sample size was small and there was considerable variation in the waking levels of cortisol (as is well documented in other studies). Nevertheless, these findings accord with the lack of change in fasting morning plasma cortisol between groups and suggest that metformin treatment had no effect on the activity of the maternal HPA axis (see *Table 6*). In addition, we found no difference in the expression of GR, 11β-HSD1 or 11β-HSD2 in the placentae of women who took metformin during pregnancy compared with those who took placebo once BMI band and mode of delivery were taken into account. In our analyses we adjusted for mode of delivery, which is recognised to alter placental gene expression of genes related to fetal glucocorticoid exposure. We acknowledge that there may be other confounding factors such as time between delivery and placental sample collection that we did not adjust for in the statistical analyses. However, all samples were collected using standard protocols and good-quality RNA was extracted from the tissues used. Although 11β-HSD2 is known to be sensitive to inflammation and we observed changes in circulating inflammatory markers at 36 weeks' gestation between women taking metformin and those taking placebo, the lack of change observed here could be consistent with a compensatory change in placental metabolism in women taking metformin. Alternatively, as our primary outcome measure of birthweight was the same in the two treatment groups, and fetal glucocorticoid exposure is a key determinant of birthweight, it is perhaps unsurprising that we have not seen an effect on this determinant of birthweight.

Myometrial contractility and glycogen storage

Introduction

Maternal obesity is well recognised to be associated with an increased risk of caesarean section.[61,140–143] Although this association is widely reported, little is known about the mechanism behind it. There is a commonly held clinical assumption that this is related to fat dystocia from the maternal tissues and/or dystocia as a result of larger babies. These are indeed likely to be contributory factors but myometrial contractility is known to be impaired in obese women, even after adjustment for birthweight.[144] Additionally, contractility is impaired in women with diabetes mellitus.[145] Of particular note is that the response to oxytocin is reduced in these women. Thus, if the diabetic environment has already reduced contractility, for example because of glycosylation of proteins and fibre damage, leading to a poorly progressing labour in these women, then oxytocin is likely to be needed. The reduced responsiveness to oxytocin would suggest that its efficacy is reduced and this may contribute to the increased rate of caesarean sections in this group of women. In addition, there is also evidence that insulin per se is detrimental to contractility, possibly by causing hyperpolarisation.[146]

Metabolic changes in the uterus are a recognised preparation for labour. These include changes in lactate dehydrogenase isoforms to those favouring hypoxic conditions and, of interest to this study, increased glycogen storage from glucose uptake into myometrial cells, along with fatty droplet inclusions.[147,148] These metabolic changes are expected to maintain forceful contraction, necessary for labour, in the face of repetitive, transient ischaemic episodes, consequent to occlusion of the blood vessels within the myometrium with each contraction. It could therefore be suggested that, if insulin sensitivity improvement occurs with metformin, then more glycogen would be stored and labour outcome improved. This suggestion can be tested directly by determining glycogen levels and also by challenging the myometrial tissue with a solution lacking glucose and monitoring contractile activity.

This mechanistic substudy was designed to examine whether or not improving insulin sensitivity with metformin improved myometrial contractility in obese pregnant women and increased myometrial glycogen content.

Methods

At caesarean section, biopsy of lower-segment myometrium was obtained from consenting women participating in the EMPOWaR trial, according to the SOP (see *Appendix 8*). All biopsies were immediately placed in physiological saline (PSS), stored at 4 °C and used for experimentation within 24 hours of collection for contractility studies or snap frozen at –80 °C for later analysis of glycogen storage.

Contractility measurements

Contractions were measured as previously described.[149] Briefly, in the laboratory, biopsies were cleared of endometrium, excess blood and any fetal membranes. Strips of myometrium 5-mm long, 2-mm wide and 1-mm thick were cut so that the longitudinal axis was aligned with the direction of the muscle fibres. Four strips were then simultaneously mounted, secured by aluminium clips, in a 1-ml chamber bath. To ensure the amount of stretch applied was standardised across experiments, all strips were placed under isometric conditions with a resting tension of 2 mN. Contractility was recorded using a tension transducer (FORT25; WPI, Sarasota, FL, USA) attached to one end of the strip, which was connected to a data acquisition system (DataTrax; WPI). The strips were superfused with PSS at a rate of 1.5 ml/minute at pH7.4 and 37 °C. Under these conditions, most strips developed a steady baseline tension and achieve spontaneous contractions within 2 hours of continual superfusion.

After strips began to contract, a control period was established of between four and six contractions, each of similar amplitude and frequency, and then strips were superfused with PSS (control), PSS lacking glucose (PSS 0-glucose) or PSS and 0.5 nM oxytocin (oxytocin) for the remainder of the experiment, as detailed below.

Measurements of mean amplitude, duration and frequency of contractions, as well as total integral of force (measured as area under the curve, AUC), were made at 30-minute intervals for each myometrial strip. Simultaneous experiments (4–12 strips per biopsy) enabled the contractility of 'test' strips to be compared with that of time-matched control strips that were contracting with similar amplitude and frequency at the start of each experiment.

Experiments in zero glucose

After 30 minutes of control contractions, test strips were bathed in PSS 0-glucose. Contractility measurements were made from test strips at 30-minute intervals and compared with those of time-matched controls.

Glycogen determination

Glycogen determination was performed following established methodologies.[148,150] Myometrial biopsy samples were snap frozen in liquid nitrogen in each hospital and stored at –80 °C. Prior to analysis, each biopsy was freeze-dried for 48 hours in a Modulyo® 4K freeze dryer (Edwards, Crawley, UK) to enable inspection and accurate dissection of approximately 10-mg aliquots of myometrium. Each aliquot was then carefully weighed and homogenised in 500 µl of water for 3 minutes (oscillation frequency of 30 Hz) using a Retsch MM 400 milling system (Haan, Germany). The homogenate was then boiled for 5 minutes to remove enzyme activity and centrifuged (at 4 °C) for 5 minutes at 13,000 g.

The lysates were analysed using a commercially obtained glycogen assay kit (Sigma-Aldrich, St Louis, MO, USA). In brief, the assay utilises a coupled enzyme reaction that hydrolyses the glycogen present in the samples into glucose. The glucose is then oxidised to yield a colorimetric product proportional to the amount of glycogen present (detectable at 570 nm) after subtraction of background signals. The lysates were diluted 10- and 20-fold in water before hydrolysis to align with the optical density range of the assay standard curve (standard glycogen concentration range 0.4–2.0 µg/well). The samples were assayed according to the manufacturer's protocol and the colorimetric product was quantified using a ThermoFisher Scientific Multiskan Ascent 354 microplate reader.

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Results

All sample collection and analysis were performed blind to treatment allocation group. Eight samples were obtained for the contractility studies. Unblinding following data lock revealed final cohort numbers as follows: placebo, $n = 2$; metformin, $n = 6$. Twenty-eight samples were obtained for the glycogen storage study with final cohort numbers as follows: placebo, $n = 17$; metformin, $n = 11$. Baseline characteristics are shown in *Table 18*.

Contractility

Responses to oxytocin were calculated and showed the expected increases in amplitude and overall force (AUC, integral). The mean increases in amplitude and force from control values (preceding spontaneous contractions, 100%) for all samples ($n = 8$) were 186% ± 21% and 216% ± 31% (standard error of the mean), respectively. In the metformin samples ($n = 6$) these values were 170% ± 12% and 210% ± 26%, respectively. In the placebo samples ($n = 2$) the averages were 261% and 296.1%, respectively (*Figure 34*).

We also examined the effects of glucose removal on the above sample (see *Figure 34*). After 120–150 minutes in PSS 0-glucose, contractions in the eight samples decreased from control values (100%) to an amplitude of 83% ± 6% and overall force (AUC) was 57% ± 9%. In the metformin samples these values were 82% ± 6% and 69% ± 10% and in the placebo samples these values were 94% and 30%, respectively.

Formal statistical analyses to compare the results between the metformin group and the placebo group were not performed because of low sample numbers.

TABLE 18 Baseline characteristics of participants in the myometrial contractility and glycogen storage substudy

	ITT		Per protocol	
Characteristic	Placebo	Metformin	Placebo	Metformin
Contractility study				
n	2	6	2	5
Age (years), mean (SD)	34.5 (7.8)	27.7 (4.3)	34.5 (7.8)	28.6 (4.0)
Gestation at delivery (days), mean (SD)	274.0 (1.4)	272.5 (3.7)	274.0 (1.4)	273.0 (3.9)
Nulliparity, *n* (%)	0 (0)	4 (66.7)	0 (0)	4 (80.0)
BMI (kg/m^2), mean (SD)	37.6 (7.1)	38.1 (3.7)	37.6 (7.1)	37.8 (4.1)
Glycogen storage study				
n	17	11	15	7
Age (years), mean (SD)	29.8 (5.8)	30 (4.7)	29.2 (5.9)	31.0 (5.0)
Gestation at delivery (days), mean (SD)	274.9 (7.7)	272.5 (4.2)	275.7 (7.6)	273.6 (3.2)
Nulliparity, *n* (%)	6 (35.3)	4 (36.4)	5 (33.3)	4 (57.1)
BMI (kg/m^2), mean (SD)	37.5 (4.6)	40.6 (4.2)	37.7 (4.7)	40.5 (4.7)

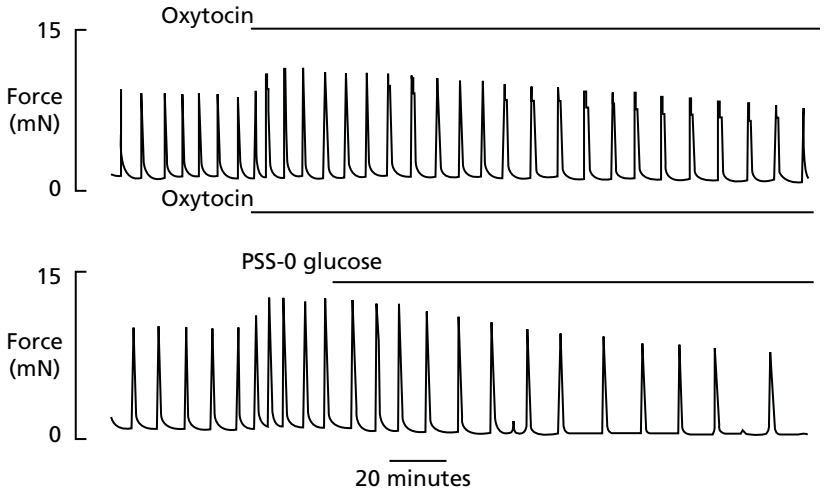


FIGURE 34 Example of myometrium contraction trace. Continuous trace of spontaneous contractions from paired strips of myometrium. Spontaneous contractions were established and then oxytocin (0.5 nM) was superfused throughout the experiment. After 30 minutes of control contractions, test strips were bathed in PSS 0-glucose.

Glycogen

Glycogen content was determined in 25 samples. Mean glycogen in myometrium was 12.8 ± 0.7 µg/mg tissue. Of the 25 samples, 13 were placebo samples and five were metformin samples, with the remaining seven samples not per the protocol. Subsequent analysis was retrospectively restricted to data obtained from compliant women. In the placebo samples ($n = 13$) mean glycogen was 13.3 ± 1.1 µg/mg and in the metformin samples ($n = 5$) it was 11.8 ± 0.7 µg/mg (unpaired *t*-test).

Discussion

It is not possible to draw any robust conclusions from this substudy as the sample size was so small and the distribution of treatment allocation following unblinding was too uneven. The unequal distribution of treatment allocations between the two groups is a consequence of an unavoidable risk when carrying out mechanistic studies blind to treatment allocation. Clearly, a large sample size will minimise the possibility of this being a problem. We had hoped to obtain a much larger sample of myometrial biopsies but the provision of expertise for 'out-of-hours' tissue collection was limited. We had anticipated that we would see improved myometrial contractility responsiveness to oxytocin and higher glycogen storage in samples from participants taking metformin. We were unable to demonstrate any differences but, as stated, our sample size was very small. There are few data on the effect of metformin on smooth muscle contractility. One small study of human myometrial biopsies did not demonstrate any differences in in vitro contractility with the addition of metformin.[151] However, there is evidence from animal models that metformin improves contractility in vascular and penile smooth muscle, mediated through activation of adenosine monophosphate-activated protein kinase or inhibition of the production of reactive oxygen intermediates.[152–155] We have previously shown impaired uterine contractility in the presence of increased cholesterol.[156] Increased cholesterol is well recognised to be associated with obesity and we hypothesised that this may be one of the contributory mechanisms behind the excess risk of caesarean delivery in obese women. In non-pregnant populations metformin has a beneficial effect on the cholesterol profile.[79] However, we did not see any effect on cholesterol in our study population and therefore it is not possible to confirm this hypothesis from these data.

Although our sample size in this substudy was insufficient to draw any conclusions, we did not see any differences in rates of caesarean section or post-partum haemorrhage in the main trial cohort, which would perhaps suggest that metformin has not had either a beneficial or an adverse effect on myometrial contractility.

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Chapter 5 Qualitative study

Introduction

Recruitment and retention of trial participants is fundamental to the success of any RCT. A high number of eligible women declined to participate in the EMPOWaR study. In addition, a number of eligible women agreed to participate, signed a consent form and underwent baseline visits and screening, but subsequently did not take trial medication or began to take trial medication and stopped.

We proposed to conduct interviews both with women who did not wish to participate and with women who consented but who did not comply with the treatment regime. However, we were able to recruit only one woman who had declined to participate in the study. Thus, our sample consisted only of women who consented to participate in the study but who did not comply with the treatment regime.

Methods

Twenty-three women who initially consented to participate in the trial but who did not comply with the treatment regime were telephoned to ask if they would participate in an interview to discuss the reasons why they had not taken the trial tablets. Of these, six women were successfully contacted and sent a recruitment pack and three women returned a signed consent form. Telephone interviews took place between February and June 2014 and were audio-recorded and transcribed with the participants' consent. Pseudonyms are used throughout.

Results

The women's ages ranged from 26 to 40 years. One of the women (Sam) was expecting her first baby when she took part in the EMPOWaR trial. A second (Penny) had two other children and the third (Janet) was pregnant with her fourth baby at the time that she was recruited to the trial.

Janet and Penny were initially offered an information sheet by their community midwife at their booking appointment and then were telephoned by a trial research midwife. Sam said that her community midwife had mentioned the study to her but no written information or referral was offered. She was telephoned later by a research midwife to discuss the study and agreed to be sent an information sheet in the post.

All three women said that they were happy to be offered information about the study. All three stated that the written information was clear and easy to understand. All three also said that they were very satisfied with the level of information given during their initial telephone conversation and in appointments with the research midwives.

The women recalled having few questions to ask the research midwives about the study. Penny said that her main question was whether or not it was safe for her to take them during pregnancy and said that she felt reassured by the answers she was given.

The reasons the women gave for agreeing to participate in the study initially were varied. Sam said that as it was her first baby she liked the idea of the extra antenatal check-ups that she would have as a result of participating in the study. She also said that she was motivated by the idea that she would be helping other women through her participation. Janet had previously participated in pregnancy-related research while attending the antenatal metabolic clinic at Edinburgh Royal infirmary in a previous pregnancy and was therefore

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familiar with the research team. She cited this as a reason for agreeing to participate in the trial. Penny said that she had a friend who had participated in the trial and who spoke positively to her about it; thus, Penny described herself as 'quite keen' and 'excited' to take part. Penny also said that she would like to help other women in the future and said that this was another reason why she agreed to take part in the study.

Sam did not take any of her trial medication. She said that when it was explained to her that she might receive a placebo she decided not to take part, as she wanted only to take an active treatment not a placebo. Sam was taking folic acid and iron tablets at the time she was recruited to the study and felt that she did not want to take a placebo tablet in addition to this. Sam said, 'If I was guaranteed a [metformin] tablet I would take it, but as it wasn't guaranteed, I thought, "no thanks" '. Sam said that she discussed her decision with her mother and her partner, but she said that she attended her trial appointments alone and it was her choice not to take the trial medication. She continued to attend her data collection appointments during pregnancy.

Janet said that she did not initially understand that the study would involve taking medication when she agreed to attend for screening. She mistakenly believed that the nature of her participation would involve only physical measurements and data collection, similar to those recorded in her previous pregnancy when she had also participated in clinical research. Janet said that she was not happy to take metformin during pregnancy. She said that, as this was her fourth baby and she had never been offered metformin during previous pregnancies, she did not feel comfortable taking it during this pregnancy. She said, 'They could do anything they wanted to me, but I wasn't willing to take any risk with my baby'. Janet spoke to her husband about the study and said that he also 'wasn't happy' for her to take the trial medication. Janet also cited the fact that she lived some distance away from the trial centre and the study necessitated several visits to the hospital as another reason for her withdrawing from the study. She said that, although she had participated in research at the same hospital in a previous pregnancy, she had only had one other child at that time. She now had three other children, making childcare arrangements during hospital visits much more challenging.

Penny took her trial tablets for approximately 5 weeks. When her pregnancy reached 21 weeks she had a premature spontaneous rupture of membranes. She was initially admitted to hospital to be monitored and said that she 'panicked' about her participation in the study. She discussed it with her husband and stopped taking the study medication. Penny continued to attend data collection appointments during her pregnancy but did not recommence trial medication.

When asked if they would participate in research in the future, all three women said that they would be willing to consider it. Penny said that she would be particularly open to participating in any trial that might help her to lose weight. Both Janet and Penny suggested that clinical community midwives should have more knowledge and information regarding pregnancy-related research, as they were not able to answer all of their questions when initially offering study information.

Discussion

It is possible that the two women in this sample who did not take the medication would have declined to participate had they fully understood the implications, risks and benefits at the time their consent was obtained. It has been observed elsewhere that participants have difficulty understanding the true meaning of a RCT and the rationale behind randomisation.[157–159] Like Sam, participants have expressed a preference for certain treatment arms.[160–162] Janet said that once she understood that she would be taking tablets during pregnancy, her concern was the potential risk of participating in the trial. Her concerns echo those of others who have declined to participate in other RCTs.[161,163]

The study sample was very small. However, the results suggest that particular attention should be given to designing appropriate trial information materials and processes that fully inform potential participants of the benefits and risks of participation. In particular, when recruiting trial participants, attention should be paid to ensuring that trial information has been understood before obtaining consent.

Chapter 6 Discussion and conclusions

Summary of findings

This was the first RCT of a pharmacological intervention, metformin, to reduce the risk of excessive birthweight offspring in non-diabetic obese pregnant women. Contrary to our hypothesis, metformin had no effect on our primary outcome of birthweight. In addition, we did not see any effect on our secondary outcomes of insulin sensitivity at 36 weeks' gestation; maternal and neonatal anthropometry; and neonatal CRP, glucose and insulin measured in cord blood. Since publishing the results of this trial[28] another group has published a similar study with a slightly smaller sample size and has again found no effect of metformin on birthweight in obese pregnant women without diabetes mellitus.[19]

The inflammatory markers CRP and IL-6 were both lower in the metformin group. These markers are known to be elevated in obese pregnant women compared with lean pregnant women[67] and may be associated with adverse pregnancy outcomes such as preterm birth and pre-eclampsia.[164,165]

Fasting glucose and insulin were lower in the metformin group at 28 weeks' gestation in the ITT analysis. On per-protocol analysis, fasting and 2-hour glucose, insulin and HOMA-IR score were all lower in the metformin group. The lack of effect at 36 weeks' gestation may reflect the changes in glucose homeostasis throughout pregnancy.

The lack of effect was evident in both the ITT and the per-protocol analyses. Our study was adequately powered and we can conclude that our results reflect a true lack of effect of the intervention, rather than a type 2 error.

Effectiveness and acceptability of the intervention

Despite the lack of an effect on our primary outcome, we believe that metformin had its expected pharmacodynamic effect given the differences in measures of insulin sensitivity at 28 weeks' gestation.

Recruitment to the trial was challenging. The majority of women declined to participate. We were unable to formally assess the reasons for this but anecdotally there is an understandable reluctance among pregnant women to take medication in pregnancy and also a lack of awareness of the potential harm associated with obesity in pregnancy.

The intervention was acceptable to the women who agreed to participate in the trial. No participants were withdrawn specifically because of treatment side effects. Overall adherence was around 60% by both diary entries and detectable levels of metformin in the 36-week blood sample. The median dose taken was 2000 g, which suggests that the treatment regimen was acceptable to most participants.

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Strengths and limitations

This was a multicentre study with a double-blind, randomised controlled design, making the findings robust and generalisable. Despite challenges with recruitment, we were still able to recruit our target sample size and we had adequate power to address our hypothesis.

We have used a recognised surrogate, birthweight centile, as a marker of future life risk of obesity in the offspring. A limitation of the study is that follow-up was limited to the early postnatal period and longer-term conclusions about the effect of metformin on the offspring will require long-term follow-up studies. Additionally, the large number of secondary outcomes means that conclusions about these results (even when $p < 0.05$) are potentially subject to a type 1 error.

We did not attempt to assess whether or not masking/blinding was effective. Metformin may cause gastrointestinal side effects and so it is possible that some women (and their caregivers) may have correctly inferred their treatment allocation from their side effect profile. However, the majority of the clinical outcomes (e.g. birthweight centile) are unlikely to be significantly affected by observer bias and so we do not think that this will have adversely affected the results.

We used a starting dose of metformin of 500 mg and a maximum dose of 2000 mg and up-titrated by 500 mg per week. In the MOP study,[19] the starting dose was 1000 mg, the maximum dose was 3000 mg and the up-titration rate was similar. In clinical practice, some clinicians up-titrate more rapidly. It is possible that different dose regimens may have produced a different result, although the MOP study also did not demonstrate any effect of metformin on the primary outcome of birthweight centile.[19]

As part of our study protocol we performed a glucose tolerance test at baseline (12–16 weeks) and excluded those who fulfilled the criteria for GDM. We anticipated that women diagnosed with GDM after enrolment would wish to withdraw and be treated with metformin as a first-line agent for their GDM. Hence, a glucose tolerance test at baseline would prevent withdrawals (and protocol violations) by identifying early women who would later be diagnosed with GDM. In practice, however, our approach has likely excluded women who are most likely to have a macrosomic baby. Glucose tolerance tests are not performed until 28 weeks in current clinical practice and so most women ultimately diagnosed with GDM have 28 weeks of pregnancy during which their babies are exposed to high levels of maternal glucose. Such women were excluded from our study.

Difficulties with recruitment reported by staff were twofold. First, although we were formally unable to quantify this, our impression was that women felt stigmatised at being identified as obese and immediately rejected the study on that basis.

Second, it was difficult to explain to potential participants the risks of maternal obesity and high birthweight for their offspring. Neither outcome was seen by women as an adverse outcome and so the concept of taking a tablet to prevent this was insufficient to overturn the generic advice not to take medications in pregnancy unless absolutely necessary.

Our study was restricted to Caucasian women to minimise the effect of ethnicity on birthweight. Over 30% of participants in the MOP study were of other ethnic groups,[19] but again no effect of metformin was seen on birthweight.

Implications for health care and recommendations for future research

Obesity is a major public health concern of our time. Rates of obesity among young women of reproductive age are ever increasing and the cycle of disadvantage is thus being perpetuated to the next generation. On the basis of this research, we can conclude that metformin should not be used to improve pregnancy outcomes in obese pregnant women without GDM. Follow-up studies of the babies born to the women who participated in the EMPOWaR trial will determine whether or not there are any longer-term benefits (or indeed harms) of metformin taken during pregnancy. Our findings of no beneficial effect are similar to those of other trials of various dietary and lifestyle interventions aimed at reducing birthweight in obese individuals. An alternative approach would be to optimise the diagnosis of GDM in obese pregnant women. Although national recommendations are that obese women should have a glucose tolerance test at 28 weeks to test for GDM, these recommendations are incompletely applied. Additionally, given that glucose levels are high in obese women from the beginning of pregnancy, deferring diagnosis until 28 weeks allows high maternal glucose to impact adversely on fetal growth for the first two-thirds of pregnancy. Hence, earlier diagnoses for GDM might be appropriate. It seems that the focus of intervention must shift towards reducing weight and optimising health in young girls and women prior to embarking on pregnancy – arguably a much greater challenge. Increasing awareness among the general public of the impact of obesity on both immediate and long-term pregnancy outcomes must also be addressed.

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Acknowledgements

This study would not have been possible without the commitment of the pregnant women who participated and we are enormously grateful to them.

We are grateful to the members of the Trial Steering Committee – Siladitya Bhattacharya (chairperson), Robbie Lindsay and Gary Mires – and the Data Monitoring Committee – Peter Brocklehurst (chairperson), Graeme MacLennan, Andrew Thomson and Catherine Williamson – who generously gave their time to support the study.

We are also grateful to the principal investigators: Derek Tuffnell (Bradford), Aamod Nawathe (Chelsea and Westminster), Janet Cresswell and Santhi Chidambaram (Chesterfield), George Bugg (Nottingham), Fiona Crosfill (Preston), Tom Farrell (Sheffield), Cally Nwosu, Sandhya Rao, Nidhi Srivastava and Vicky Cording (Whiston); the study midwives: Julie Grindey (Arrowe Park), Diane Farrar, Vicky Jones, Jennifer Syson, Gillian Butterfield, Rebecca Palethorpe and Tracey Germaine-Rylance (Bradford), Kathryn McCormick and Sarah Ladd (Chelsea and Westminster), Mary Kelly-Baxter, Louise Underwood and Claire Wood (Chesterfield), Lynsdey Prue and Natasha Kaba (Coventry), Jennifer Devlin, Yvonne Grieg, Hayley Moir, Alice Keeley and Mary Simpson (Edinburgh), Falak Diab, Caroline Cunningham and Katherine Day (Liverpool Women's Hospital), Natasha Singh and Suzanne Ridley (Imperial), Yvonne Toomassi, Yvette Davis and Yvette Gunn (Nottingham), Katrina Rigby (Preston), Pam Inniss (Royal Blackburn), Hilary Rosser, Siobhan Gillespie, Sarah Senbeto, Alison Carey and Anne Chamberlain (Sheffield), Jane Hillen and Debbie Bullen (University Hospitals Coventry and Warwickshire), Lauren Lacey (University College London), Zoe Grindlay (Whitson); and the pharmacists: Kathryn Hayes (Blackburn), Martin Shepherd (Chestefield), Hazel Milligan (Edinburgh), Elaine Willis (Liverpool Women's Hospital), Margaret Hargreaves (Whitson) and Louise Hough (Preston).

We are grateful to Nanette Hibbert, Graham Harrold, Rose Leask, Ana Calarrao, Forbes Howie and Linda Nicol for providing expert technical assistance; to Ruth Andrew, Natalie Homer and Sanjay Kothiya for their expertise in gas chromatography mass spectrometry; and to Karen Noble for carrying out the myometrial work. We are grateful to the staff at the Clinical Research Imaging Centre, Edinburgh, particularly Annette Cooper (senior magnetic resonance radiographer) and her team for carrying out the MRI scans and Dr Jane Walker (consultant radiologist) for reviewing the scans for clinical reporting. We are also grateful to Allan Walker and Garry Milne for their help in generating the database and Lorraine Adamson, Tariq Derdeb and Carolyn Newton for excellent administrative assistance. Finally, we are grateful to the administrators in participating NHS research and development departments and to all others who have helped with the study but who we have been unable to name.

Funding

This study was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council (MRC) and NIHR partnership (grant reference number 08/246/09). The EME programme is funded by the MRC and NIHR, with contributions from the Chief Scientist Office in Scotland and National Institute for Social Care and Health Research in Wales and the Health and Social Care Research and Development Division, Public Health Agency in Northern Ireland.

Active and placebo treatments were supplied without charge by Merck KGaA and we are grateful to them. Neither the funder nor the supplier of the active and placebo drugs had any role in study design, data collection, data analysis, data interpretation or writing of the report. The joint study sponsor in terms of the European Union Clinical Trials Directive was the University of Edinburgh and NHS Lothian and had no role in analysis of the data. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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Contributions of authors

Carolyn A Chiswick wrote the manuscript. **Carolyn A Chiswick**, **Rebecca M Reynolds**, **Fiona C Denison**, **Amanda J Drake**, **Shareen Forbes**, **David E Newby**, **Brian R Walker**, **Siobhan Quenby**, **Andrew Weeks**, **Hany Lashen**, **Sonia Whyte**, **Natalie Homer** and **Jane E Norman** acquired the data. Rebecca M Reynolds, Fiona C Denison, Amanda J Drake, Shareen Forbes, David E Newby, Brian R Walker, Siobhan Quenby, **Susan Wray**, **Gordon D Murray**, Sonia Whyte and Jane E Norman designed the study. Susan Wray and **Karen Noble** carried out the analysis and interpretation of the myometrial contractility and glycogen storage studies. **Aryelly Rodriguez** and Gordon D Murray analysed the data. **Ruth Andrew** provided expertise in analysis and interpretation of the gas chromatography–mass spectrometry and liquid chromatography–mass spectrometry data. **Scott Semple** and **Calum Gray** provided expertise for the analysis and interpretation of the MRI data. **Marian C Aldhous** carried out the analysis for the placental 11β-HSD1 and 2 and glucocorticoid receptor studies. **Sarah Cunningham-Burley** and **Alice Keely** were responsible for the qualitative study. Jane E Norman conceived the study. All authors interpreted the data, revised the manuscript critically for important intellectual content and approved the final version.

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Data sharing statement

All available data can be obtained from the corresponding author.

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Appendix 1 Study protocol

The study protocol can be found at www.nets.nihr.ac.uk/projects/eme/0824609 (accessed 11 July 2016).

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Appendix 2 Maternal anthropometry measurements

EMPOWAR Skin fold Measurements (Anthropometry)
Working Practice Document (WPD)

EMPOWAR WPD number: 3

Version: 1.0

Author: Sonia Whyte, Trial Manager

Authorised by: [redacted]

Prof. Jane E. Norman

Date authorised: *29th June 2012*

Effective Date: *29th June 2012*

1. PURPOSE

The purpose of this WPD is to describe the process for measuring height, waist, hip, Mid arm and mid thigh measurements along with the skin folds of adult participants in the EMPOWaR study and to ensure that all participating sites are consistent in their methods of gathering measurements. This document should be retained in the ISF section 7

2. DEFINITIONS

ISF Investigator Site File

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PI Principle investigator at the site

WPD Working Practice Documents

3. WHY

The specific guidelines for taking anthrpometric measurements are created as it helps ensure accuracy and repeatability for future testing across the participating sites

4. WHO

All staff delegated by the PI for the task of taking the measurements will receive training, if required, in how to collect the measurements.

5. PROCEDURE

Equipment required:

- A height meter
- A tape measure.
- A Harpenden skinfold calipers
- A pen with water soluble ink for marking the participants' skin

Technique for height measurement:

Participant should be instructed to remove shoes and hair ornaments. The following position is necessary:

- Feet together
- Feet flat on the ground
- Heels touching the back plate of the measuring instrument
- Legs must be straight
- Buttocks against the backboard
- Scapula, wherever possible, against the backboard
- Arms loosely at side

The head must be positioned with the lower margins of the orbit in the same horizontal plane as the external auditory meati, i.e. the corner of the eyes horizontal to the middle of the ear. The participant is asked to look straight ahead.

The head piece of the measuring tape should be lowered so that the hair is pressed flat. If the participant is taller than the measurer, the measurer should stand on a platform so that he/she can properly read the height rule. Note: self reported height is not acceptable. The result is recorded in cm, to the nearest 0.5 cm.

Technique for waist measurement

Ideally a metal or paper measuring tape should be used, as they will not stretch.

Position of waist circumference measurement: Waist circumference should be measured at a level midway between the lower rib margin and iliac crest with the tape all around the body in a horizontal position.

- Participants are asked to remove their clothes, except for light underwear. If this is not possible, for example due to cultural reasons, the alternative is to measure the circumference on the subject without heavy outer garments and record this fact in the study database.

- The measurer should stand at the side of the participant in order to have a clear view of the tape.

- Participants should be standing with their feet fairly close together (about 12-15 cm) with their weight equally distributed to each leg. Participants are asked to breathe normally; the reading of the measurement should be taken at the end of gentle exhaling. This will prevent subjects from contracting their abdominal muscles or from holding their breath.

- The measuring tape is held firmly, ensuring its horizontal position. Verify that the tape position is horizontal all around the waist. The tape should be loose enough to allow the observer to place one finger between the tape and the subject's body. The result is recorded in cm, to the nearest 0.5 cm.

Technique for hip circumference measurement

- Position of hip circumference measurement: Hip circumference should be measured as the maximal circumference over the buttocks. The tape position should be horizontal around the body.
- The same technique as for waist circumference, except for tape position, is followed. The result is recorded in cm, to the nearest 0.5 cm.

Technique for left mid-arm circumference measurement

- The arm is relaxed and hanging by the side, and the circumference is taken at the level of the mid-point between the acromial (boney point of shoulder) and the olecranon (boney point of elbow) processes.
- When recording, you need to make sure the tape is not too tight or too loose, is lying flat on the skin, and is horizontal. The result is recorded in cm, to the nearest 0.5 cm.

Technique for left mid-thigh circumference measurement

- First mark the site to be measured. The subject stands erect with their weight evenly distributed on both feet and legs slightly parted.

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- The circumference measure is taken at the level of the mid-point on the lateral (outer side) surface of the thigh, midway between trochanterion (top of the thigh bone, femur) and tibiale laterale (top of the tibia bone).
- When recording, you need to make sure the tape is not too tight or too loose, is lying flat on the skin, and with the tape horizontal. The result is recorded in cm, to the nearest 0.5 cm.

Technique for skin fold measurements:

- Measurement should be taken on healthy, undamaged and uninfected dry skin. Moist skin is harder to grasp and can influence the measurement. Do not use the Caliper on broken or infected skin.
- Mark the skinfold location using a pen with water soluble ink. Use a tape measure to accurately find the mid-points.
- The final value recorded should be the average of the two that seems best to represent the skinfold fat site.
- Experience is necessary to grasp the same size skinfold in the same location consistently. Practice these techniques until you get consistent results.
- Keep the Caliper clean using a lint free cloth and ensure that they are stored in dry conditions to prevent corrosion.
- Do not use any spirit based cleaner on the Caliper as this may cause damage to the plastic materials.

6. RELATED DOCUMENTS AND REFERENCES

SKIN FOLD MEASUREMENT PROCESS IN ADULT PARTICPANTS

General Notes

1. Instruct the test subject to keep the muscles relaxed during the test.
2. Take all measurements on the **left** side of the body.
3. Consider use of tape measure to accurately find the mid-points at the four sites (see below).
4. Grasp skinfold between thumb and index finger. Gently pull the skinfold away from the body. (In practice it may be helpful to ask the subject to tense up the muscle first then grip skinfold to ensure that no muscle is grasped and then ask them to relax).
5. The Caliper should be placed perpendicular to the fold, approximately 1cm below the finger and thumb. While maintaining the grasp of the skinfold, allow the Caliper to be released so that full tension is placed on the skinfold. The dial should be read to the nearest 0.50mm, 1 to 2 seconds after.

6. Measure at least 2 times at each site.
7. Record the average of the two folds that best represent the skinfold site.

Landmarks of Sites:

Site 1 – Biceps: The anterior surface of the biceps midway between the anterior axillary fold and the antecubital fossa.

Site 2 – Triceps: A vertical fold on the posterior midline of the upper arm, over the triceps muscle, halfway between the acromion process and olecranon process. The elbow should be extended and the arm relaxed.

Site 3 – Subscapular: The fold is taken at 45 degrees (to the vertebrae) to 1-2cm below the inferior angle of the scapulae and 1-2cm toward the arm.

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Appendix 3 Neonatal anthropometry measurements

EMPOWAR Measurement of Skinfold Thickness of Babies and Young Children (WPD)

EMPOWAR WPD number:	4
Version:	1.0
Author:	Kay Riding, Lead Paediatric Research Nurse
Adapted for EMPOWAR by:	Sonia Whyte, Trial Manager
Authorised by:	_____
	Prof. Jane E. Norman
	_____
Date authorised:	09th April 2012
Effective Date:	09th April 2012

1. PURPOSE

The purpose of this WPD is to describe the procedure for the correct technique to perform skinfold thickness measurements with babies / young children thus ensuring that results are accurate and repeatable. It should be retained in section 7 of the ISF.

2. DEFINITIONS

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ISF Investigator Site File
PI Principle investigator at the site
RM Research Midwife
RN Research Nurse
WPD Working Practice Document

3. WHY

The WPD supports EMPOWAR research site staff delegated by the PI to perform skinfold thickness measurements with babies / young children. Standardisation of the measurement is essential for collection of accurate readings.

4. WHO

This WPD applies to all site staff delegated to undertaking skinfold thickness measurements with babies / young children for the EMPOWaR Study.

All staff undertaking this measurement should have received relevant training prior to commencing the study. The Harpenden skinfold calliper will be used to undertake this measurement. It is the responsibility of the site staff allocated to the study to ensure the Callipers are working correctly.

5. PROCEDURE

5.1 Ensure that the skinfold calliper dial is set at zero each time before use.

5.2 Explain the procedure to the parent / carer. Demonstrate the procedure on the back of the parent's / carer's hand.

5.3 Ask parent / carer to remove the baby's / young child's upper clothing.

5.4 **Subscapular Skinfold**

5.4.1 Lay the baby prone on the parent's / carer's lap or on a changing mat on the bed. If the child is old enough the measurement should be taken in the sitting position.

5.4.2 The measurement point for the subscapular skinfold located immediately below the inferior angle of the scapula is identified by palpating and marking the inferior angle of the scapula.

5.4.3 The skinfold is picked up between their finger and thumb of the researcher 1 cm above and medial to the subscapular mark, the callipers are then applied to the 'neck' of the fold over the mark so that the fold runs diagonally down toward the left elbow.

5.4.4 While maintaining a grip on the skinfold, the calliper handles should be released gently allowing the jaws of the calliper to close on the fat fold for 2 seconds before taking the reading to the last completed 0.2 mm.

5.5 **Triceps Skinfold**

5.5.1 Babies / young children should be held by a parent / carer.

5.5.2 The mid-upper-arm is the point used to measure triceps skinfold. It is half the distance between the acronium process and the olecranon. To find the mid point, the shoulder should be palpated to find the acromion, the baby's / young person's arm should then be bent at 90 degree at the elbow to identify the olecranon. The distance between the two should be measured and a small horizontal mark made at the midpoint on the posterior aspect of the arm prior to removing the tape measure. Ideally two people are required to undertake this part of the procedure.

5.5.3 The left arm should hang relaxed at the side or be held down by parent / carer or assistant.

5.5.4 Standing behind the baby / young person the researcher should pick up the skinfold between their finger and thumb about 1 cm above the midpoint mark over the triceps muscle, with the fold running downward along the midline of the back upper arm. The callipers are then applied at right angles to the 'neck of the fold just below the finger and thumb over the mid point mark.

5.5.5 While maintaining a grip on the skinfold, the calliper handles should be released gently allowing the jaws of the calliper to close on the fat fold for 2 seconds before taking the reading to the last completed 0.2 mm.

6. RELATED DOCUMENTS AND REFERENCES

'Measurement and standardisation protocols for anthropometry used in the construction of a new international growth reference.' de Onis, M *et al* 2004. Food and Nutrition Bulletin, vol 25, no1

'Anthropometry training video' May 2004, WHO Multicentre Growth Reference Study (http://www.who.int/childgrowth/training/en/) CRFSOP 15.101 A v01 Clinical Research Facility, Edinburgh

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Appendix 4 Collection, storage and transfer of blood samples



EMPOWAR Blood sampling collection

Working Practice Document (WPD)

EMPOWAR WPD number:	5
Version:	3.0
Author:	Dr. Fiona Denison Sonia Whyte
Revised:	
Authorised by:	[redacted] Prof. Jane E. Norman
Date authorised:	25th January 2013
Effective Date:	28th January 2013

1. PURPOSE

The purpose of this WPD is to describe the process for collecting and preparing the blood samples for adult participants in the EMPOWaR study and to ensure that all participating sites are consistent in their methods of collection and storage. This document should be retained in the ISF, section 7

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NB: It is import this document is reviewed in conjunction with the current version of the study protocol to ensure all samples collected and all tests required are obtained, as the protocol may be more up to date.

2. DEFINITIONS

Hr – Hour
Inc. - Including
ISF - Investigator Site File
Mins - Minutes
PI - Principle investigator at the site
t - Time
WPD - Working Practice Documents
Trial Research Laboratories – Edinburgh

3. WHY

The specific guidelines for taking blood samples are created to help ensure accuracy and repeatability across the participating sites.

4. WHO

This WPD applies to all staff delegated by the PI for the task of collecting and preparing samples.

5. PROCEDURE

Collected between 10-0 and 16+0 weeks gestation prior to randomisation

1. Prepare the following tubes for sampling at baseline (0hr) and 2 hours (2hr + or- 5 Mins).

Timing	Reagent	Volume	Number	Analysis	Processing
0hr	Fluoride oxalate	2.7mls	1	Glucose	To hospital

					laboratories
0hr	Serum gel	7.5mls	1	Renal function, LFTs, lipid profile, CRP	To hospital laboratories
0hr	Serum gel	7.5mls	1	Cortisol, insulin, NEFA	To trial research laboratories
0hr	EDTA	9mls	1	Adipokines, inflammatory markers Fatty acids in red cell membranes	To trial research laboratories
0hr	Lithium heparin	4.7mls	1	Adipokines, inflammatory markers	To trial research laboratories
2hr	Fluoride oxalate	2.7mls	1	Glucose	To hospital laboratories

TOTAL VOLUME BLOOD (MAX): 34.1mls

2. Label tubes for NHS lab using hospital identification (ID), date and time of collection. For research tubes, write research number on tubes, date of collection and gestation.

3. Check subject has fasted from midnight.

4. Venepuncture

- Identify proposed site of venepuncture and apply a tourniquet to upper arm, 15cms above venepuncture site.
- Find a vein and clean site with antiseptic wipe. Ask patient to clench and open fist three times, using a needle collect blood and fill all tubes required at t=0hr.
- Leaving the needle in place release tourniquet.
- Apply cotton wool to puncture site and withdraw needle, discard into sharps bin.
- Apply pressure to the puncture site until bleeding has stopped. Apply a plaster if required.
- Gently invert each blood tube a few times to mix the blood and reagent. (Shaking too much or violently will lyse the red cells).

Collect the tubes in the following order of priority: fluoride oxalate, serum gel (FOR HOSPITAL LABS), serum gel EDTA, lithium heparin, (FOR TRIAL RESEARCH LABS),

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5. Send one fluoride oxalate tube and one serum gel tube to the NHS laboratories and complete the request form asking for glucose, U+E, LFT, lipid profile and CRP.
6. Place remaining tubes on (not in) ice for later processing.
7. Record the t=0hr time and request the subject to drink a 75g oral glucose load within 10Mins
8. At t=2hr (+ or – 5mins) repeat the venepuncture and send the fluoride oxalate tube to NHS hospital lab for analysis of 2hr glucose. Label tube with hospital ID, date and time of collection.
9. Deliver bagged and labelled samples collected for the trial research labs on ice or in a chill bag to the designated local lab for sample processing and storage.

28 weeks gestation

1. Prepare the following tubes for sampling at baseline (0hr) and 2 hours (2hr).

Timing	Reagent	Volume	Number	Analysis	Processing
0hr	Fluoride oxalate	2.7mls	1	Glucose	To hospital laboratories
0hr	Serum gel	7.5mls	1	CRP	To hospital laboratories
0hr	Serum gel	7.5mls	1	Cortisol, insulin, NEFA	To trial research laboratories
0hr	EDTA	9mls	1	Adipokines, inflammatory markers Fatty acids in red cell membranes	To trial research laboratories
0hr	Lithium heparin	4.7mls	1	Adipokines, inflammatory markers	To trial research laboratories
2hr	Fluoride oxalate	2.7mls	1	Glucose	To hospital laboratories

TOTAL VOLUME BLOOD (MAX): 34.1mls

2. Label tubes for NHS lab using hospital ID, date and time of collection. For research tubes, write research number on tubes, date of collection and gestation.

3. Check subject has fasted from midnight

4. Venepuncture

- Identify proposed site of venepuncture and apply a tourniquet to upper arm, 15cms above venepuncture site.
- Find a vein and clean site with antiseptic wipe. Ask patient to clench and open fist three times, using a needle collect blood and fill all tubes required at t=0hr.
- Leaving the needle in place release tourniquet.
- Apply cotton wool to puncture site and withdraw needle, discard into sharps bin.
- Apply pressure to the puncture site until bleeding has stopped. Apply a plaster if required.
- Gently invert each blood tube a few times to mix the blood and reagent. (Shaking too much or violently will lyse the red cells).

Collect the tubes in the following order of priority: fluoride oxalate, serum gel (TO HOSPITAL LAB), serum gel, EDTA and lithium heparin (TO TRIAL RESEARCH LAB).

5. Send one fluoride oxalate tube and one serum gel tube to the NHS laboratories and complete the request form asking for glucose and CRP.

6. Place remaining tubes on (not in) ice for later processing.

7. Record the t=0hr time and request the subject to drink a 75g oral glucose load within 10Mins.

8. At t=2hr repeat (+ or – 5mins) the venepuncture and send the fluoride oxalate tube to hospital lab for analysis of 2hr glucose. Label tube with hospital ID, date and time of collection.

9. Deliver bagged and labelled samples collected for the trial research labs on ice or in a chill bag to the designated local lab for sample processing and storage.

36 weeks gestation

1. Prepare the following tubes for sampling at baseline (0hr) and 2 hours (2hr).

Timing	Reagent	Volume	Number	Analysis	Processing
0hr	Fluoride oxalate	2.7mls	1	Glucose	To hospital laboratories
0hr	Serum gel	7.5mls	1	Renal function, LFTs, lipid profile, CRP	To hospital laboratories

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0hr	Serum gel	7.5mls	1	Cortisol, insulin, NEFA	To trial research laboratories
0hr	EDTA	9mls	1	Adipokines, inflammatory markers Fatty acids in red cell membranes	To trial research laboratories
0hr	Lithium heparin	4.7mls	1	Adipokines, inflammatory markers	To trial research laboratories
2hr	Fluoride oxalate	2.7mls	1	Glucose	To hospital laboratories

TOTAL VOLUME BLOOD (MAX): 34.1mls

2. Label tubes for NHS lab using hospital ID, date and time of collection. For research tubes, write research number on tubes, date of collection and gestation.

3. Check subject has fasted from midnight

4. Venepuncture

- Identify proposed site of venepuncture and apply a tourniquet to upper arm, 15cms above venepuncture site.
- Find a vein and clean site with antiseptic wipe. Ask patient to clench and open fist three times, using a needle collect blood and fill all tubes required at t=0hr.
- Leaving the needle in place release tourniquet.
- Apply cotton wool to puncture site and withdraw needle, discard into sharps bin.
- Apply pressure to the puncture site until bleeding has stopped,. Apply a plaster if required.
- Gently invert each blood tube a few times to mix the blood and reagent. (Shaking too much or violently will lyse the red cells).

Collect the tubes in the following order of priority. fluoride oxalate, serum gel (TO HOSPITAL LAB), serum gel, EDTA and lithium heparin (TO TRIAL RESEARCH LABS).

5. Send one fluoride oxalate tube and one serum gel tube to the NHS laboratories and complete the request form asking for glucose and CRP.

6. Place remaining tubes on (not in) ice for later processing.

7. Record the t=0hr time and request the subject to drink a 75g oral glucose load within 10Mins.8..At t=2hr repeat (+ or – 5mins) the venepuncture and send the fluoride oxalate tube to hospital lab for analysis of 2hr glucose. Label tube with hospital ID, date and time of collection.

9. Deliver bagged and labelled samples collected for the trial research labs on ice or in a chill bag to the designated local lab for sample processing and storage.

Procedure FOR COLLECTING CORD BLOODS

1. Ensure that the tubes for cord blood gases required by the NHS Trust/Board and (if the donor is Rhesus Negative) cord blood for Group and Save have been collected.

2. Use the cord clamps to isolate a loop of umbilical cord.

Reagent	Volume	Number	Analysis	Processing
Fluoride oxalate	2.7mls	1	Glucose	To hospital laboratories
Serum gel	2.7mls	1	CRP	To hospital laboratories
EDTA	4.7mls	1	Adipokines, inflammatory markers Fatty acids in red cell membranes	To trial research laboratories
Serum gel	2.7mls	1	Cortisol, C-peptide, NEFA	To trial research laboratories
Lithium heparin	2.7mls	1	Adipokines, inflammatory markers	To trial research laboratories

3. Ideally collect bloods within 15 minutes of delivery.

In order of priority, collect the following tubes from the cord vessels (ideally venous): fluoride oxalate, serum gel (to hospital labs), EDTA, serum gel and lithium heparin (to trial research labs).

4. Ensure tubes appropriately labelled. Store samples on ice and transport to the laboratory.

4. Transport blood samples at 4°C (on ice) collected for the trial research labs to the designated local lab for sample processing and storage.

Sample processing

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1. When the bloods are collected they should be processed immediately or at least spun as soon as possible after collection. Samples for Insulin analysis are required to be kept at 4°C.

2. Spin the blood tubes at 2,200rpm for 10 min at +4°C.

3. Remove the tubes from the centrifuge and carefully remove the plasma or serum layer using a pastette pipette and aliquot a minimum of 0.5ml aliquots into pre-labelled 2.0ml screw-top tubes using the maximum of 6 tubes.

5. The white layer in the Plasma EDTA tubes is the buffy coat and is kept for DNA extraction. Pipette carefully this layer into a 2.0ml screw-top tube prelabelled BUFFY. Some red cell or plasma contamination is acceptable. The easiest way to isolate this is to dislodge it from the tube wall using a pipette then slowly suck it out the tube.

6. Aliquot ~0/5ml of remaining red blood cells (RBC) into a separate pre-labelled 2.0 ml screw-top tube.This sample is kept for the analysis of fatty acids in red cell membranes.

In summary the maximum sample set per participant visit should consist of:

6 EDTA plasma samples
6 Lithium Heparin plasma samples
6 Serum samples
1 Buffy sample
1 RBC sample

If only a small amount of blood is collected during a visit less samples tubes may be prepared.

Please ensure all tubes are correctly labelled and freeze them at -20°C or -80°C until subsequent analysis.

NB: Labels should include: the reagent used to collect the sample e.g. EDTA/Lith Hep/serum gel), Buffy (where appropriate), RBC (where appropriate) date of sample collection, subject study ID and gestation

Transfer of frozen samples to the University of Edinburgh

The research team at the University of Edinburgh should be contacted to arrange receipt of the samples before any arrangements are made for transfer (see contact details below).

Samples sent should be transferred with a copy of the EMPOWaR tissue collection log Please review WPD 10 Transport of samples for further details.

Contact details to arrange the collections:

Sonia Whyte

EMPOWaR Trial Manager

xxxxxxx

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Appendix 5 Serious adverse event form

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Academic and Clinical Central Office for Research and Development

NHS Lothian

SERIOUS ADVERSE EVENT (SAE) FORM (CTIMP) **DO NOT SEND PATIENT IDENTIFIABLE DATA OR SOURCE DOCUMENTS WITH THIS FORM**			
Study name:		**Participant ID:**	
EudraCT number:		**Date of report (dd/mm/yyyy):**	

TO BE COMPLETED BY ACCORD (*INTERNAL USE ONLY*)	
Date of Receipt:	
Information Complete: ☐ Yes ☐ No *Initials:*	Follow-up Requested: ☐ Yes ☐ No Details:

1. REPORT DETAILS		
Centre ID:	**Centre name:**	**Country SAE reported from:**
Report stage: Initial ☐	**Submitted** (dd/mm/yyyy):	**Date PI first notified of SAE** (dd/mm/yyyy):
Report stage: Follow-up ☐	**Submitted** (dd/mm/yyyy):	

2. EVENT DETAILS	
Date of onset (dd/mm/yyyy):	**Diagnosis:**
Description of SAE in medical terms:	

Seriousness Criteria (check all that are relevant to the event):

☐ Participant died
☐ Inpatient hospitalisation or prolongation of existing inpatient hospitalisation
☐ Life-threatening
☐ Involved persistent or significant disability or incapacity
☐ Congenital anomaly/ birth defect
☐ Other significant medical event

Other SAE criteria:

☐ Recommendation of the DMC
☐ New events/reactions likely to affect the safety of participants
☐ Post study SUSAR

Severity of event: ☐ Mild ☐ Moderate ☐ Severe

Is the event due to progression of underlying disease? ☐Yes ☐No
Is the event due to a lack of efficacy of IMP? ☐Yes ☐No
If yes, please indicate which IMP(s):

ACCORD, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ
Fax: [redacted] Email: [redacted]
CR005-T01v3.1

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Academic and Clinical Central Office for Research and Development
NHS Lothian

SERIOUS ADVERSE EVENT (SAE) FORM (CTIMP) ***DO NOT SEND PATIENT IDENTIFIABLE DATA OR SOURCE DOCUMENTS WITH THIS FORM***			
Study name:		**Participant ID:**	
EudraCT number:		**Date of report (dd/mm/yyyy):**	

3. STUDY TREATMENT

IMP(s) (if blinded, suspected IMP)	Dose /schedule	Route of administration	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy) or tick box if ongoing	Causally Related to IMP? *Tick either unrelated or possibly related*		Expected (Y/N)
					Unrelated	Possibly Related	
1.				☐			
2.				☐			
3.				☐			

4. NIMPs (Non-investigational medicinal products)

Are there any additional medications **used as part of the protocol** (e.g. rescue medications or escape medications for the study IMP)? *Such medications are referred to as NIMPs*

Yes ☐ No ☐

If yes, please complete the table below

NIMP(s)	Dose/ schedule	Route of administration	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy) or tick box if ongoing	Causally Related to NIMP? *Tick either unrelated or possibly related*		Expected (Y/N/NA)
					Unrelated	Possibly Related	
1.				☐			
2.				☐			
3.				☐			

5. CONCOMITANT DRUGS RELEVANT TO THE SAE

☐Tick box if no relevant concomitant medication

Drug name	Dose/schedule	Route of administration	Reason for use	Start date (dd/mm/yyyy)	End date (dd/mm/yyyy)	Continued? (Y/N)
1.						
2.						
3.						
4.						

6. MEDICAL HISTORY *(list relevant medical history)*

☐Tick box if no relevant medical history

Condition	Start Date (dd/mm/yyyy)	End date (dd/mm/yyyy)	Ongoing (Y/N)	Medication required Y/N
1.				
2.				
3.				
4.				

7. RELEVANT TEST/LABORATORY FINDINGS *(include only the results relevant to the SAE diagnosis or course of SAE)*

☐Tick box if no relevant tests

Test/lab finding	Unit	Date (dd/mm/yyyy)	Value	Date (dd/mm/yyyy)	Value	Date (dd/mm/yyyy)
1.						

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Fax: [redacted] Email: [redacted]
CR005-T01v3.1

accord Academic and Clinical Central Office for Research and Development NHS Lothian

SERIOUS ADVERSE EVENT (SAE) FORM (CTIMP) **DO NOT SEND PATIENT IDENTIFIABLE DATA OR SOURCE DOCUMENTS WITH THIS FORM**			
Study name:		**Participant ID:**	
EudraCT number:		**Date of report (dd/mm/yyyy):**	

2.						
3.						
4.						

Comment on test/laboratory findings (if none, mark as NA)

8. ACTION TAKEN *(section may be updated for follow up reports)*		
☐ IMP permanently discontinued: *If multiple IMPs used, please record which IMP(s) have been discontinued:* Date discontinued (dd/mm/yyyy): *Initial and date (dd/mm/yyyy):*	☐ IMP dose reduced *If multiple IMPs used, please record which IMP(s) have been reduced:* Date reduced (dd/mm/yyyy): *Initial and date (dd/mm/yyyy):*	☐ IMP dose increased *If multiple IMPs used, please record which IMP(s) have been increased:* Date increased (dd/mm/yyyy): *Initial and date (dd/mm/yyyy):*
☐ IMP dose not changed *Initial and date (dd/mm/yyyy):*	☐ Unknown *Initial and date (dd/mm/yyyy):*	☐ Not applicable *Initial and date (dd/mm/yyyy):*

9. OUTCOME OF SAE *(section may be updated for follow up reports)*		
☐ Completely recovered: Date recovered (dd/mm/yyyy): *Initial and date (dd/mm/yyyy):*	☐ Condition still present and unchanged *Initial and date (dd/mm/yyyy):*	☐ Recovered with sequelae: Date recovered (dd/mm/yyyy): *Initial and date (dd/mm/yyyy):*
☐ Condition deteriorated *Initial and date (dd/mm/yyyy):*	☐ Condition improving *Initial and date of initial (dd/mm/yyyy):*	☐ Death: Date of death (dd/mm/yyyy): Post mortem? Yes ☐ No ☐ *Initial and date (dd/mm/yyyy):*

ACCORD, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ
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NHS Lothian

SERIOUS ADVERSE EVENT (SAE) FORM (CTIMP) ***DO NOT SEND PATIENT IDENTIFIABLE DATA OR SOURCE DOCUMENTS WITH THIS FORM***			
Study name:		**Participant ID:**	
EudraCT number:		**Date of report (dd/mm/yyyy):**	

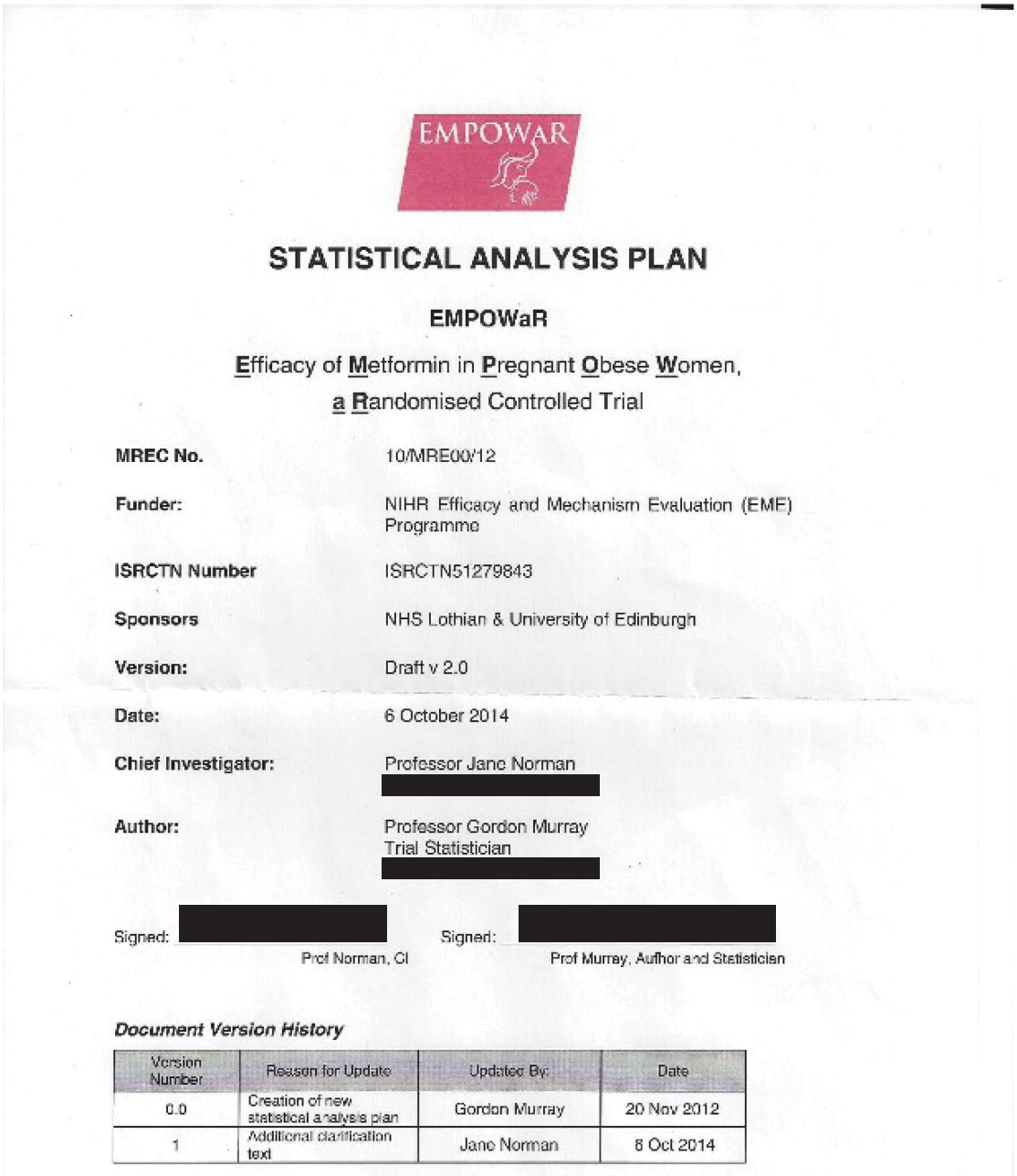
10. ADDITIONAL INFORMATION

11. INFORMATION SOURCE FOR INITIAL REPORT			
Name, address, telephone number and email address of person completing report:			
PI name:			
PI signature:		Date: dd/mm/yy	
ALL REPORTS MUST BE SIGNED AND DATED BY THE PRINICPAL INVESTIGATOR. PLEASE SCAN TO .pdf AND E-MAIL REPORTS TO ACCORD ([redacted]) ALTERNATIVELY, PLEASE FAX REPORTS TO ACCORD ON [redacted]			

12. INFORMATION SOURCE FOR FINAL FOLLOW UP REPORT			
Name, address, telephone number and email address of person completing report:			
PI name:			
PI signature:		Date: dd/mm/yy	
ALL REPORTS MUST BE SIGNED AND DATED BY THE PRINICPAL INVESTIGATOR. PLEASE SCAN TO .pdf AND E-MAIL REPORTS TO ACCORD ([redacted]) ALTERNATIVELY, PLEASE FAX REPORTS TO ACCORD ON [redacted]			

ACCORD, Queen's Medical Research Institute, 47 Little France Crescent, Edinburgh EH16 4TJ
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CR005-T01v3.1

Appendix 6 Statistical analysis plan



EMPOWaR

STATISTICAL ANALYSIS PLAN

EMPOWaR

Efficacy of Metformin in Pregnant Obese Women,
a Randomised Controlled Trial

MREC No.	10/MRE00/12
Funder:	NIHR Efficacy and Mechanism Evaluation (EME) Programme
ISRCTN Number	ISRCTN51279843
Sponsors	NHS Lothian & University of Edinburgh
Version:	Draft v 2.0
Date:	6 October 2014
Chief Investigator:	Professor Jane Norman [redacted]
Author:	Professor Gordon Murray Trial Statistician [redacted]

Signed: [redacted] Signed: [redacted]

Prof Norman, CI Prof Murray, Author and Statistician

Document Version History

Version Number	Reason for Update	Updated By:	Date
0.0	Creation of new statistical analysis plan	Gordon Murray	20 Nov 2012
1	Additional clarification text	Jane Norman	6 Oct 2014

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EMPOWaR: Efficacy of Metformin in Pregnant Obese Women, a Randomised Controlled Trial

Funding reference number: 08/246/09 (NIHR Efficacy and Mechanism Evaluation Programme)
EudraCT number 2009-017134-47

Statistical Report

Population = Intention to treat (ITT) - AllocatedTreatment used for analysis

Report number: 02

Confidential

Data set analysed as it was on:
29 April 2015

EMPOWaR Statistical Report (AllocatedTreatment used) - tables run on: 05MAR2016

By: Aryelly Rodriguez - ECTU Statistician

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Section 1. Disposition / data checks

1.1 Patient disposition before randomisation - All Centres

Parameter(s)	*Categories*	*---Overall--- Count (n(%)*
All patients in DB (n(%))	Yes	4867 (100)
Declined reason (n(%))	Subject participate has declined	2861 (58.8)
	Other Reason	57 (1.2)
	Failed Exclusion	100 (2.1)
	Failed Inclusion	626 (12.9)
	Failed both Exclu and Inclu	4 (0.1)
	Did not decline and pass IN_EX but not rand*	10 (0.2)
	Did not attend appointment	8 (0.2)
	Unable to contact	752 (15.5)
	Did not decline and pass IN_EX and rand	449 (9.2)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
n = number of observations
*These patients (13045 13053 13084 13102 13117 13121 13122 13123 13168 13189) were screened as eligible, but then they subsequently declined or were no longer contactable
NOTE:These patients (11562 11892 13047 13065) were randomised but also have a reason to decline

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Section 1. Disposition / data checks

1.2.1.1 Patient disposition after randomisation - All Centres

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Consented/randomised (n(%))	Yes	223 (100)	226 (100)	449 (100)
Disposition in database (n(%))	Active	196 (87.9)	191 (84.5)	387 (86.2)
	Declined	2 (0.9)	2 (0.9)	4 (0.9)
	Withdrawn by clinician	0	1 (0.4)	1 (0.2)
	Lost to follow up	9 (4.0)	7 (3.1)	16 (3.6)
	Participant withdrawn	15 (6.7)	24 (10.6)	39 (8.7)
	Serious Adverse Event	1 (0.4)	1 (0.4)	2 (0.4)
Outcome (z score) available* (n(%))	Yes - Live Birth	218 (97.8)	213 (94.2)	431 (96.0)
	Yes - Live Birth-followed by neonatal death	2 (0.9)	1 (0.4)	3 (0.7)
	Yes - Stillbirth	0	2 (0.9)	2 (0.4)
	No - Miscarriage	0	4 (1.8)	4 (0.9)
	No - Termination of Pregnancy	2 (0.9)	1 (0.4)	3 (0.7)
	No - Not available	1 (0.4)	5 (2.2)	6 (1.3)
Outcome (Glucose test) avalilable# (n(%))	Yes	148 (66.4)	142 (62.8)	290 (64.6)
	No	75 (33.6)	84 (37.2)	159 (35.4)

N = number of patients randomised, n = number of observations

*Available at visit 8 (Delivery) - the latest date of delivery (DOD) was 14JUL2014, for Patient 13508 outcome was miscarriage and for Patient 12074 outcome was alive birth, these labels were assigned post database lock

#Available at visit 6 (36 Weeks) - checks: test date, base value and two hr value must be present

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Section 1. Disposition / data checks

1.2.1.2 Patient disposition after randomisation - All Centres - Consort figures

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Treatment distributed(n(%))	Data available	222 (99.6)	225 (99.6)	447 (99.6)
	Withdrawn pre treatment	1 (0.4)	1 (0.4)	2 (0.4)
Outcome (z score) available* (n(%))	Data available	220 (98.7)	214 (94.7)	434 (96.7)
	Stillbirth	0	2 (0.9)	2 (0.4)
	Miscarriage (<24 weeks)	0	4 (1.8)	4 (0.9)
	Withdrawn pre treatment	1 (0.4)	1 (0.4)	2 (0.4)
	Withdrawn post treatment	0	3 (1.3)	3 (0.7)
	Lost to follow up	0	1 (0.4)	1 (0.2)
	Termination of Pregnancy	2 (0.9)	1 (0.4)	3 (0.7)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
N = number of patients randomised, n = number of observations
*Available at visit 8 (Delivery)
IMPORTANT NOTES on manual identification:
Patients 12046 and 12047 withdrawn pre treatment
Patients 17063, 27317 and 18113 withdrawn post treatment
Patients 12041, 12086 and 21119 were identified as miscarriage but they were termination of pregnacies TOP

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Section 1. Disposition / data checks

1.2.1.2 Patient disposition after randomisation - All Centres - Consort figures (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Follow up Visit 9 data available* (n(%))	Data available	128 (57.4)	132 (58.4)	260 (57.9)
	Miscarriage (<24 weeks)	0	4 (1.8)	4 (0.9)
	Did not attend the visit	65 (29.1)	54 (23.9)	119 (26.5)
	Decline to further participate	16 (7.2)	20 (8.8)	36 (8.0)
	Lost to follow up	9 (4.0)	7 (3.1)	16 (3.6)
	Withdrawn pre treatment	1 (0.4)	1 (0.4)	2 (0.4)
	Withdrawn post treatment	0	3 (1.3)	3 (0.7)
	Withdrawn by clinician	0	1 (0.4)	1 (0.2)
	Stillbirth	0	2 (0.9)	2 (0.4)
	Termination of Pregnancy	2 (0.9)	1 (0.4)	3 (0.7)
	Live Birth followed by neonatal death	2 (0.9)	1 (0.4)	3 (0.7)

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N = number of patients randomised, n = number of observations

*Available at visit 9 (3 months postnatal)

IMPORTANT NOTES on manual identification:

Patients 15028, 12053 and 14145 were alive births but died after delivery (from SAE forms)

Section 1. Disposition / data checks

1.2.2 Study Populations - All Centres

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Randomised - ITT population (n(%))*	Yes	223 (100)	226 (100)	449 (100)
IMP at least once (n(%))#	Missing	46	59	105
	No	8 (4.5)	9 (5.4)	17 (4.9)
	Yes	169 (95.5)	158 (94.6)	327 (95.1)
Compliant - PP population (n(%))$	Missing	46	59	105
	No	59 (33.3)	58 (34.7)	117 (34.0)
	Yes	118 (66.7)	109 (65.3)	227 (66.0)

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N = number of patients randomised, n = number of observations
*The intention to treat (ITT) population will comprise all randomised subjects
#Members of the ITT population who took IMP at least once
$The per-protocol (PP) population will comprise those members of the ITT population who completed the study without a major protocol violation and who complied adequately with the randomised treatment, further details of treatment compliance are in table 3.2.2 of this report

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DOI: 10.3310/eme03070

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Section 1. Disposition / data checks

1.3 Patient disposition - Minimisation variables

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Centres (n(%))	Royal Infirmary of Edinburgh	60 (26.9)	59 (26.1)	119 (26.5)
	Coventry	49 (22.0)	49 (21.7)	98 (21.8)
	Liverpool Womens Hospital	38 (17.0)	39 (17.3)	77 (17.1)
	Sheffield	24 (10.8)	24 (10.6)	48 (10.7)
	Notts City	7 (3.1)	6 (2.7)	13 (2.9)
	Notts QMC	8 (3.6)	6 (2.7)	14 (3.1)
	Bradford	4 (1.8)	4 (1.8)	8 (1.8)
	St Helens	1 (0.4)	3 (1.3)	4 (0.9)
	Chelsea and Westminster	0	1 (0.4)	1 (0.2)
	Preston	18 (8.1)	18 (8.0)	36 (8.0)
	Arrow Park Wirral	3 (1.3)	4 (1.8)	7 (1.6)
	Chesterfield	11 (4.9)	12 (5.3)	23 (5.1)
	Blackburn	0	1 (0.4)	1 (0.2)
BMI band at randomisation*(n(%))	30-39 Kg/m^2	152 (68.2)	152 (67.3)	304 (67.7)
	>40 Kg/m^2	71 (31.8)	74 (32.7)	145 (32.3)

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N = number of patients randomised, n = number of observations

*For patients 11693 and 17059, BMI was calculated at randomisation using the height in m instead of cm, as a consequence the results were respectively 375390 and 352955 kg/m^2 and these patients landed in the >40 kg/m^2 BMI band, their calculated BMI were 37.5 and 35.50 kg/m^2

Section 1. Disposition / data checks

1.4 Data Completeness by time point

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Patients CRF Completeness by CRF SECTIONS	*Allocated Regimen*			
	METFORMIN		*PLACEBO*	
	Visit attended		*Visit attended*	
	Yes	*No*	*Yes*	*No*
VISIT 1 (SCREENING)	226	0	223	0
VISIT 2 (BASELINE)	226	0	223	0
VISIT 3 (RANDOMISATION)	226	0	223	0
VISIT 4 (18 TO 20 WEEKS)	194	32	188	35
VISIT 5 (28 WEEKS)	175	51	183	40
VISIT 6 (36 WEEKS)	145	81	158	65
VISIT 7 (TERM)	73	153	76	147
VISIT 8 (DELIVERY)	201	25	206	17
VISIT 9 (FINAL)	132	94	128	95

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DOI: 10.3310/eme03070

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Section 1. Disposition / data checks

1.4 Data Completeness by time point

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Patients CRF Completeness by CRF SECTIONS	*Allocated Regimen* *OVERALL* *Visit attended*	
	Yes	*No*
VISIT 1 (SCREENING)	449	0
VISIT 2 (BASELINE)	449	0
VISIT 3 (RANDOMISATION)	449	0
VISIT 4 (18 TO 20 WEEKS)	382	67
VISIT 5 (28 WEEKS)	358	91
VISIT 6 (36 WEEKS)	303	146
VISIT 7 (TERM)	149	300
VISIT 8 (DELIVERY)	407	42
VISIT 9 (FINAL)	260	189

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.1 Maternal Age

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Maternal Age at consent (years)	Mean	28.9	28.7	28.8
	Median	29.0	28.0	29.0
	SD	5.1	5.8	5.5
	MIN,MAX	17,43	18,43	17,43
	Q1,Q3	25,33	24,33	24,33
	n	223	226	449
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.2 Maternal Life Style Status

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Smoking Status (n(%))	ACTIVE	31 (13.9)	40 (17.7)	71 (15.8)
	PREVIOUSLY	13 (5.8)	15 (6.6)	28 (6.2)
	NOT SMOKING	179 (80.3)	171 (75.7)	350 (78.0)
Alcohol During Pregnancy (n(%))	Yes	9 (4.0)	3 (1.3)	12 (2.7)
	No	214 (96.0)	223 (98.7)	437 (97.3)
Illicit Drug Status (n(%))	USING	1 (0.4)	0	1 (0.2)
	NOT USING	222 (99.6)	226 (100)	448 (99.8)

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.3 Maternal Education

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Educational Qualifications (n(%))	No formal qualifications	17 (7.6)	8 (3.5)	25 (5.6)
	Entry level certification/foundation diploma	7 (3.1)	12 (5.3)	19 (4.2)
	GCSE, Standard grade, "O" grades	55 (24.7)	55 (24.3)	110 (24.5)
	A level, A/S level, Highers or BTEC Dip/Cert.	49 (22.0)	37 (16.4)	86 (19.2)
	Cert. higher Education, City & Guilds	15 (6.7)	14 (6.2)	29 (6.5)
	Diploma HE/FE or HND/HNC	30 (13.5)	30 (13.3)	60 (13.4)
	Graduate certificate or Diploma	4 (1.8)	9 (4.0)	13 (2.9)
	Degree	32 (14.3)	47 (20.8)	79 (17.6)
	Professional Qualification	3 (1.3)	4 (1.8)	7 (1.6)
	PGCE/Postgraduate certificate or Diploma, Masters. Doctorate	11 (4.9)	10 (4.4)	21 (4.7)
Educational Qualifications coded (n(%))	None	17 (7.6)	8 (3.5)	25 (5.6)
	School up to 16 years	62 (27.8)	67 (29.6)	129 (28.7)
	School 16 to 18 years	64 (28.7)	51 (22.6)	115 (25.6)
	College or Uni degree or Higher	80 (35.9)	100 (44.2)	180 (40.1)

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.4.1 Previous pregnacy status* PARITY 1

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
PARITY1 (n(%))	0	84 (37.7)	100 (44.2)	184 (41.0)
	=>1	139 (62.3)	126 (55.8)	265 (59.0)

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.4.2 Previous pregnacy status*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Number of Previous Pregnancies (n(%))	Missing	3	0	3
	0	59 (26.8)	79 (35.0)	138 (30.9)
	1	66 (30.0)	61 (27.0)	127 (28.5)
	2	46 (20.9)	47 (20.8)	93 (20.9)
	3	20 (9.1)	21 (9.3)	41 (9.2)
	4	12 (5.5)	9 (4.0)	21 (4.7)
	5	11 (5.0)	2 (0.9)	13 (2.9)
	6	3 (1.4)	3 (1.3)	6 (1.3)
	7	2 (0.9)	3 (1.3)	5 (1.1)
	8	0	1 (0.4)	1 (0.2)
	9	1 (0.5)	0	1 (0.2)
At least one Prev Preg* (n(%))	Missing	3	0	3
	Yes	161 (73.2)	147 (65.0)	308 (69.1)
	No	59 (26.8)	79 (35.0)	138 (30.9)

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N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 12 weeks or more were considered regardless of outcome and if a patient had more than one previous pregnancy, only her latest pregnancy was counted

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.4.3 Previous Pregnancy details*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Multiple Pregnancy#(%)	Missing	3	0	3
	Yes	4 (2.5)	6 (4.1)	10 (3.2)
	No	157 (97.5)	141 (95.9)	298 (96.8)
Gestation of Pregnancy#(weeks)(n(%))	Missing	3	0	3
	<12	40 (24.8)	38 (25.9)	78 (25.3)
	12<22	2 (1.2)	5 (3.4)	7 (2.3)
	>22	119 (73.9)	104 (70.7)	223 (72.4)
Last Pregnancy Outcome#(%)	Missing	3	0	3
	Miscarriage	31 (19.3)	32 (21.8)	63 (20.5)
	Ectopic	1 (0.6)	1 (0.7)	2 (0.6)
	Termination of Pregnancy	9 (5.6)	10 (6.8)	19 (6.2)
	Live Birth	120 (74.5)	103 (70.1)	223 (72.4)
	Live Birth followed by neonatal death	0	1 (0.7)	1 (0.3)
Pre term Birth#(n(%))	Missing	26	27	53
	Yes	8 (5.8)	6 (5.0)	14 (5.4)
	No	130 (94.2)	114 (95.0)	244 (94.6)

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N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 12 weeks or more were considered regardless of outcome and if a patient had more than one previous pregnancy, only her latest pregnancy was counted

#Only summarised for patiens who has a previous pregnancy in the previous table

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.5 Maternal Blood Pressure at baseline

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Maternal Systolic BP (mmHg)	Mean	119.4	117.6	118.5
	Median	120.0	118.0	120.0
	SD	10.4	10.8	10.6
	MIN,MAX	90,142	91,148	90,148
	Q1,Q3	111,127	110,126	110,126
	n	223	226	449
	Nmiss	0	0	0
Maternal Diastolic BP (mmHg)	Mean	68.9	68.0	68.5
	Median	69.0	69.0	69.0
	SD	7.3	7.8	7.6
	MIN,MAX	50,90	49,86	49,90
	Q1,Q3	64,74	60,74	62,74
	n	223	226	449
	Nmiss	0	0	0

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DOI: 10.3310/eme03070

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.6 Current pregnancy details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Ultrasound Confirmation (n(%))	Yes	219 (98.2)	224 (99.1)	443 (98.7)
	No	4 (1.8)	2 (0.9)	6 (1.3)
Gestation at baseline* (days)	Mean	98.9	99.1	99.0
	Median	100.0	99.0	100.0
	SD	8.7	8.1	8.4
	MIN,MAX	71,112	70,112	70,112
	Q1,Q3	92,106	94,106	93,106
	n	223	226	449
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Gestation at this time point shold be between 70 and 112 days

Section 2. Baseline - Visit 2 (10-16 Weeks) - Putative father

2.2.1 Putative father Age

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Paternal age (years)	Mean	31.5	31.3	31.4
	Median	31.0	31.0	31.0
	SD	6.3	6.7	6.5
	MIN,MAX	15,50	20,60	15,60
	Q1,Q3	27,35	26,36	26,36
	n	221	221	442
	Nmiss	2	5	7

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Putative father

2.2.2 Putative father Height and Weight

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Paternal height (cm)	Mean	178.5	177.1	177.8
	Median	178.0	178.0	178.0
	SD	8.3	13.7	11.3
	MIN,MAX	156,207	63,196	63,207
	Q1,Q3	173,185	173,185	173,185
	n	204	202	406
	Nmiss	19	24	43
Paternal weight (Kg)	Mean	92.3	93.5	92.9
	Median	89.3	89.0	89.0
	SD	22.5	25.8	24.2
	MIN,MAX	57,154	57,205	57,205
	Q1,Q3	74,105	76,105	76,105
	n	187	188	375
	Nmiss	36	38	74

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 2. Baseline - Visit 2 (10-16 Weeks) - Putative father

2.2.3 Putative father Ethnicity

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Ethnic Origin (n(%))	Missing	0	2	2
	White	214 (96.0)	210 (93.8)	424 (94.9)
	Non-White	9 (4.0)	14 (6.3)	23 (5.1)
Ethnic Origin-More detail (n(%))	Missing	0	2	2
	White	214 (96.0)	210 (93.8)	424 (94.9)
	Mixed	4 (1.8)	4 (1.8)	8 (1.8)
	Asian	0	3 (1.3)	3 (0.7)
	Black	4 (1.8)	6 (2.7)	10 (2.2)
	Othe Ethnic group	1 (0.4)	1 (0.4)	2 (0.4)

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Medical history

2.3.1 Preeclampsia or Hypertension / Hypertension Requiring Treatment

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Preeclampsia or Hypertension (n(%))	Yes	7 (3.1)	10 (4.4)	17 (3.8)
	No	216 (96.9)	216 (95.6)	432 (96.2)
Currently taking Medication (n)	Yes	0	1	1
	No	7	9	16
Hypertension Require Treatment (n(%))	Yes	2 (0.9)	1 (0.4)	3 (0.7)
	No	221 (99.1)	225 (99.6)	446 (99.3)
Currently taking Medication (n)	No	2	1	3

Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Medical history

2.3.2 Polycystic Ovarian Syndrome / Depression Requiring Treatment

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Polycystic Ovarian Syndrome (n(%))	Yes	21 (9.4)	28 (12.4)	49 (10.9)
	No	201 (90.1)	196 (86.7)	397 (88.4)
	Unk	1 (0.4)	2 (0.9)	3 (0.7)
Currently taking Medication (n)	No	21	28	49
Depression Require Treatment (n(%))	Yes	71 (31.8)	48 (21.2)	119 (26.5)
	No	152 (68.2)	178 (78.8)	330 (73.5)
Currently taking Medication (n)	Yes	9	11	20
	No	62	37	99

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Medical history

2.3.3 Anxiety Requiring Treatment / Use of Steriods

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Anxiety Require Treatment (n(%))	Yes	20 (9.0)	15 (6.6)	35 (7.8)
	No	203 (91.0)	211 (93.4)	414 (92.2)
Currently taking Medication (n)	Yes	5	4	9
	No	15	11	26
Use of Steriods (n(%))	Yes	22 (9.9)	13 (5.8)	35 (7.8)
	No	201 (90.1)	213 (94.2)	414 (92.2)
Currently taking Medication (n)	Yes	18	11	29
	No	4	2	6

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Family history

2.4 Any family history for the following conditions

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Medical History* (n(%))	Yes	142 (63.7)	157 (69.5)	299 (66.6)
	No	78 (35.0)	67 (29.6)	145 (32.3)
	Unk	3 (1.3)	2 (0.9)	5 (1.1)
Cardiovascular disease (n(%))	Yes	69 (30.9)	71 (31.4)	140 (31.2)
	No	150 (67.3)	152 (67.3)	302 (67.3)
	Unk	4 (1.8)	3 (1.3)	7 (1.6)
Diabetes(n(%))	Yes	101 (45.3)	99 (43.8)	200 (44.5)
	No	120 (53.8)	124 (54.9)	244 (54.3)
	Unk	2 (0.9)	3 (1.3)	5 (1.1)
Preeclampsia(n(%))	Yes	22 (9.9)	19 (8.4)	41 (9.1)
	No	198 (88.8)	200 (88.5)	398 (88.6)
	Unk	3 (1.3)	7 (3.1)	10 (2.2)
Any other medical history(n(%))	Yes	96 (43.0)	109 (48.2)	205 (45.7)
	No	127 (57.0)	117 (51.8)	244 (54.3)

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N = number of patients randomised, n = number of observations

*In order to be yes, at least one condition below must be present, for no all conditions below must be also no

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.1 Mother Anthropometry / Height and Weight*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Maternal Height (cm)	Mean	165.1	165.5	165.3
	Median	165.0	165.0	165.0
	SD	5.9	5.9	5.9
	MIN,MAX	149,184	152,182	149,184
	Q1,Q3	161,170	162,170	161,170
	n	223	226	449
	Nmiss	0	0	0
Maternal Weight (kg)	Mean	102.94	103.60	103.27
	Median	99.20	101.35	100.20
	SD	17.00	15.50	16.25
	MIN,MAX	72.0,170.4	74.0,154.8	72.0,170.4
	Q1,Q3	90.1,111.9	93.0,113.5	92.0,112.1
	n	223	226	449
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.2 Mother Anthropometry / BMI_c and Waist*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Maternal BMI Calculated (kg/m^2)	Mean	37.699	37.751	37.725
	Median	36.659	36.882	36.787
	SD	5.598	4.935	5.269
	MIN,MAX	30.12,61.27	30.03,57.23	30.03,61.27
	Q1,Q3	33.14,40.88	34.17,41.10	33.61,41.01
	n	223	226	449
	Nmiss	0	0	0
Maternal Waist (cm)	Mean	108.69	110.09	109.39
	Median	106.00	109.00	108.00
	SD	13.50	11.86	12.71
	MIN,MAX	64.0,152.0	84.0,145.0	64.0,152.0
	Q1,Q3	99.0,117.0	102.0,117.0	100.0,117.0
	n	222	225	447
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.3 Mother Anthropometry / Hip and MidArm*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Maternal Hip (cm)	Mean	126.38	127.39	126.89
	Median	125.00	126.00	125.00
	SD	12.12	11.78	11.95
	MIN,MAX	95.0,159.0	100.0,160.5	95.0,160.5
	Q1,Q3	117.0,133.5	119.0,135.0	118.0,134.0
	n	222	225	447
	Nmiss	1	1	2
Maternal Mid Arm (cm)	Mean	36.29	36.74	36.51
	Median	36.00	36.00	36.00
	SD	5.01	4.65	4.83
	MIN,MAX	20.0,54.0	27.5,52.0	20.0,54.0
	Q1,Q3	33.0,39.0	34.0,39.4	33.5,39.0
	n	220	221	441
	Nmiss	3	5	8

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.4 Mother Anthropometry / Mid Thigh and Tricep Skinfold*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Maternal Mid Thigh (cm)	Mean	64.15	64.24	64.20
	Median	64.00	63.00	64.00
	SD	7.67	6.91	7.29
	MIN,MAX	25.0,84.0	50.0,89.0	25.0,89.0
	Q1,Q3	60.0,69.0	60.0,68.0	60.0,68.5
	n	219	222	441
	Nmiss	4	4	8
Maternal Tricep Skinfold (mm)	Mean	31.176	31.936	31.556
	Median	30.550	31.000	30.800
	SD	9.666	10.793	10.241
	MIN,MAX	5.00,62.00	8.00,66.00	5.00,66.00
	Q1,Q3	25.00,37.80	24.00,39.00	24.50,38.00
	n	222	222	444
	Nmiss	1	4	5

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.5 Mother Anthropometry / Bicep Skinfold and Subscapular Skinfold*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Maternal Bicep Skinfold (mm)	Mean	25.707	27.432	26.570
	Median	24.200	25.800	25.000
	SD	9.998	10.890	10.478
	MIN,MAX	1.00,60.00	9.00,61.00	1.00,61.00
	Q1,Q3	20.00,31.00	20.00,34.00	20.00,32.00
	n	222	222	444
	Nmiss	1	4	5
Maternal Subscapular Skinfold (mm)	Mean	31.997	32.555	32.275
	Median	32.700	31.300	32.000
	SD	12.205	11.805	11.998
	MIN,MAX	3.00,67.80	8.00,71.00	3.00,71.00
	Q1,Q3	24.00,40.00	24.50,39.00	24.00,39.00
	n	222	220	442
	Nmiss	1	6	7

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 3. Compliance

3.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated* Gestation - Visit 1 (days)	Mean	86.1	86.0	86.1
	Median	87.0	88.0	88.0
	SD	14.0	13.6	13.8
	MIN,MAX	47,112	51,112	47,112
	Q1,Q3	79,97	77,95	79,96
	n	223	226	449
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	98.9	99.1	99.0
	Median	100.0	99.0	100.0
	SD	8.7	8.1	8.4
	MIN,MAX	71,112	70,112	70,112
	Q1,Q3	92,106	94,106	93,106
	n	223	226	449
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value, repeated from table 2.1.6, shown here just for completeness

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Section 3. Compliance

3.1 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks) (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated* Gestation - Visit 3 (days)	Mean	101.1	100.8	101.0
	Median	102.0	101.0	102.0
	SD	8.1	7.4	7.7
	MIN,MAX	84,118	84,113	84,118
	Q1,Q3	95,108	96,108	95,108
	n	223	226	449
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	142.0	143.7	142.9
	Median	141.0	141.0	141.0
	SD	13.9	29.1	22.9
	MIN,MAX	102,252	114,498	102,498
	Q1,Q3	135,145	134,145	135,145
	n	197	202	399
	Nmiss	26	24	50

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 3. Compliance

3.1 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks) (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated* Gestation - Visit 5 (days)	Mean	197.6	197.6	197.6
	Median	197.0	197.0	197.0
	SD	9.0	6.0	7.7
	MIN,MAX	155,275	167,226	155,275
	Q1,Q3	195,200	195,200	195,200
	n	192	184	376
	Nmiss	31	42	73
Calculated* Gestation - Visit 6 (days)	Mean	252.9	251.4	252.2
	Median	253.0	253.0	253.0
	SD	8.7	24.4	18.0
	MIN,MAX	155,264	-43,268	-43,268
	Q1,Q3	251,256	251,256	251,256
	n	165	154	319
	Nmiss	58	72	130

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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Section 3. Compliance

3.1 Gestation by timepoint - Visit 7 Term (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated* Gestation - Visit 7 (days)	Mean	284.3	278.8	281.5
	Median	278.0	279.0	278.0
	SD	72.8	18.6	52.4
	MIN,MAX	155,1011	250,419	155,1011
	Q1,Q3	273,281	274,280	274,280
	n	109	115	224
	Nmiss	114	111	225
Calculated* Gestation - Visit 8 (days)	Mean	278.9	278.3	278.6
	Median	281.0	280.0	280.0
	SD	26.1	30.5	28.4
	MIN,MAX	132,459	99,527	99,527
	Q1,Q3	272,288	271,287	271,287
	n	218	218	436
	Nmiss	5	8	13

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 3. Compliance

3.1 Gestation by timepoint - Visit 8 Delivery (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Recorded* Gestation - Visit 8 (days)	Mean	274.7	275.0	274.9
	Median	277.5	278.0	278.0
	SD	20.4	18.3	19.3
	MIN,MAX	130,298	126,297	126,298
	Q1,Q3	271,286	271,285	271,286
	n	222	218	440
	Nmiss	1	8	9
Coded R_gestation - Visit 8 (n(%))	Missing	1	8	9
	<= 24 WEEKS	2 (0.9)	2 (0.9)	4 (0.9)
	>24 and <=37 WEEKS	14 (6.3)	19 (8.7)	33 (7.5)
	>37 WEEKS	206 (92.8)	197 (90.4)	403 (91.6)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Actual recorded value

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Section 3. Compliance

3.2.1 Treatment compliance / Tablets returned by study visit

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Tablets Returned Visit 5 (28 Weeks) (n(%))	Missing	66	80	146
	Yes	13 (8.3)	9 (6.2)	22 (7.3)
	No	144 (91.7)	137 (93.8)	281 (92.7)
Tablets Returned Visit 8 (Delivery) (n(%))	Missing	42	37	79
	Yes	69 (38.1)	79 (41.8)	148 (40.0)
	No	112 (61.9)	110 (58.2)	222 (60.0)

Section 3. Compliance

3.2.2 Treatment compliance Calculated using the patient diary (as per SAP)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated Compliance* (n(%))	Missing	46	59	105
	No	59 (33.3)	58 (34.7)	117 (34.0)
	Yes	118 (66.7)	109 (65.3)	227 (66.0)

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N = number of patients randomised, n = number of observations

*The number of weeks that a patient was pregnant within the study period was calculated using the gestation at baseline and the gestation at delivery, this value was then halved and compared to the number of weeks recorded in the diary, if a patient has less week diary entries than the halved total weeks then she is non-compliant straight away. If a patient had equal or more week diary entries than halved total weeks then it was required that she taken at least one pill for 4 days in order to declare a compliant week. Finally for being treatment compliant the patient should have equal or more than 50% of compliant weeks out of all available weeks

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Section 3. Compliance

3.2.3.1 Cross Check* of Treatment compliance Calculated# vs tablets returned - Visit 5 (28 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Compliance by tablets retuned at visit 5	Allocated Regimen			
	METFORMIN		PLACEBO	
	Tablets returned		Tablets returned	
	Yes	No	Yes	No
Compliance				
No	3	30	3	38
Yes	6	92	9	89

Compliance by tablets retuned at visit 5	Allocated Regimen	
	OVERALL	
	Tablets returned	
	Yes	No
Compliance		
No	6	68
Yes	15	181

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N = number of patients randomised, n = number of observations

*This table is just a compleness check and its outcome did not affect the ITT, safety or the PP population

#Compliance is explained in table 3.2.2 of this report

Section 3. Compliance

3.2.3.2 Cross Check* of Treatment compliance Calculated# vs tablets returned - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Compliance by tablets retuned at visit 8	Allocated Regimen			
	METFORMIN		PLACEBO	
	Tablets returned		Tablets returned	
	Yes	No	Yes	No
Compliance				
No	15	34	11	37
Yes	57	43	53	46

Compliance by tablets retuned at visit 8	Allocated Regimen	
	OVERALL	
	Tablets returned	
	Yes	No
Compliance		
No	26	71
Yes	110	89

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N = number of patients randomised, n = number of observations

*This table is just a compleness check and its outcome did not affect the ITT, safety or the PP population

#Compliance is explained in table 3.2.2 of this report

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Section 3. Compliance

3.3 Treatment compliance / Metformin level in blood samples at Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Metformin level (ng/mL)	Mean	2.3	61.5	31.2
	Median	0.0	7.0	0.0
	SD	16.2	172.5	124.5
	MIN,MAX	0,154	0,1611	0,1611
	Q1,Q3	0,0	0,48	0,10
	n	137	131	268
	Nmiss	86	95	181
Any Metformin level coded (n(%))	Missing	86	95	181
	Yes	12 (8.8)	80 (61.1)	92 (34.3)
	No	125 (91.2)	51 (38.9)	176 (65.7)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 3. Compliance

3.4 Cross Check* of Treatment compliance Calculated# vs Metformin level in blood samples at Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Compliance by metformin level at visit 6	Allocated Regimen			
	METFORMIN		PLACEBO	
	Any Metformin		Any Metformin	
	Yes	No	Yes	No
Compliance				
No	13	20	3	28
Yes	63	20	7	86

Compliance by metformin level at visit 6	Allocated Regimen	
	OVERALL	
	Any Metformin	
	Yes	No
Compliance		
No	16	48
Yes	70	106

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N = number of patients randomised, n = number of observations

*This table is just a compleness check and its outcome did not affect the ITT, safety or the PP population

#Compliance is explained in table 3.2.2 of this report and in the SAP

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Section 4. Secondary Outcome - All Patients

4.1.1.1.1.1 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Parameter(s)	*Categories*	*---------Allocated_Intervention---------* *Placebo N=223*	*Metformin N=226*	*Overall N=449*
Delivery Method (n(%))	Missing	1	7	8
	Spontaneous vaginal delivery	126 (56.8)	133 (60.7)	259 (58.7)
	LSCS in labour	34 (15.3)	25 (11.4)	59 (13.4)
	LSCS pre labour	42 (18.9)	40 (18.3)	82 (18.6)
	Forceps/ventouse	18 (8.1)	21 (9.6)	39 (8.8)
	Vaginal breech	2 (0.9)	0	2 (0.5)
C-SECTION index pregnancy (n(%))	Missing	1	7	8
	Yes	76 (34.2)	65 (29.7)	141 (32.0)
	No	146 (65.8)	154 (70.3)	300 (68.0)
Primary C-SECTION in index pregancy (n(%))	Missing	1	7	8
	Yes	46 (20.7)	42 (19.2)	88 (20.0)
	No	176 (79.3)	177 (80.8)	353 (80.0)

Section 4. Secondary Outcome - All Patients

4.1.1.1.1.2 Birth Outcome - C-SECTION current pregnancy - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of CSECTIONYN by AllocatedTreatment

CSECTIONYN(C-section coded (Y/N))	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
Missing	7	1	.
Yes	65	76	141
No	154	146	300
Total	219	222	441

Frequency Missing = 8

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
c_section_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.811	0.543	1.211	0.3056	0.3095

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*Analised using logistic regression (binary logit), probability modeled is csec='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_1_1_c_section.lst'

By: Aryelly Rodriguez - ECTU Statistician

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Section 4. Secondary Outcome - All Patients

4.1.1.1.1.3 Birth Outcome - First ever C-SECTION - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of first_c_section by AllocatedTreatment*

first_c_section(First ever c-section in current pregnancy (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Missing	7	1	.
Yes	42	46	88
No	177	176	353
Total	219	222	441

Frequency Missing = 8

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
first_csec_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.908	0.569	1.449	0.6853	0.7216

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*Analised using logistic regression (binary logit), probability modeled is first_csec='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_1_1_c_section.lst'

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Section 4. Secondary Outcome - All Patients

4.1.1.1.2.1 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Delivery Blood Loss (mL)	Mean	494.9	486.7	490.8
	Median	400.0	400.0	400.0
	SD	405.5	453.7	429.5
	MIN,MAX	100,2500	50,5000	50,5000
	Q1,Q3	250,600	300,580	250,600
	n	216	212	428
	Nmiss	7	14	21
Hemorrhage* (n(%))	Missing	7	14	21
	Yes	21 (9.7)	20 (9.4)	41 (9.6)
	No	195 (90.3)	192 (90.6)	387 (90.4)
SAE recorded due to Hemorrhage# (n(%))	Missing	1	1	2
	Yes	10	8	18
	No	10	11	21

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N = number of patients randomised, n = number of observations

*Hemorrhage defined as a blood loss greater than 1000ml

#Only summarised for patients with hemorrhage=yes in the item right above

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Section 4. Secondary Outcome - All Patients

4.1.1.1.2.2 Birth Outcome - Hemorrhage - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of HEMORRHAGE by AllocatedTreatment

HEMORRHAGE(Heamorrhage (Y/N))	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
Missing	14	7	.
Yes	20	21	41
No	192	195	387
Total	212	216	428

Frequency Missing = 21

Parameter(s)	*Studied effects*		*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
HEMORRHAGE_itt	AllocatedTreatment	METFORMIN vs PLACEBO	0.967	0.508	1.842	0.9193	1.0000

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*Analised using logistic regression (binary logit), probability modeled is Hemorr='Yes'
#Significance level set at p<0.05
Detailed analysis in file 'Empowar_4_1_1_1_postpartum_hemorrhage_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 4. Secondary Outcome - All Patients

4.1.1.1.3 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Parameter(s)	*Categories*	*---------Allocated_Intervention---------* *Placebo N=223*	*Metformin N=226*	*Overall N=449*
Labour Type (n(%))	Missing	2	6	8
	Spontaneous	89 (40.3)	97 (44.1)	186 (42.2)
	Induced	98 (44.3)	82 (37.3)	180 (40.8)
	C-section	34 (15.4)	41 (18.6)	75 (17.0)
Non Spontaneous Reason* (n(%))	Missing	3	8	11
	Post dates	24 (18.3)	16 (13.2)	40 (15.9)
	Pre-eclampsia	3 (2.3)	6 (5.0)	9 (3.6)
	Abruption	0	1 (0.8)	1 (0.4)
	Other maternal condition	45 (34.4)	48 (39.7)	93 (36.9)
	Previous C-section	20 (15.3)	16 (13.2)	36 (14.3)
	Previous obstetric history (other)	4 (3.1)	2 (1.7)	6 (2.4)
	Maternal request	10 (7.6)	5 (4.1)	15 (6.0)
	Suspected fetal compromise	13 (9.9)	13 (10.7)	26 (10.3)
	Malpresentation	5 (3.8)	8 (6.6)	13 (5.2)
	Suspected IUGR	3 (2.3)	2 (1.7)	5 (2.0)
	Suspected Macrosomia	4 (3.1)	4 (3.3)	8 (3.2)

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N = number of patients randomised, n = number of observations

*Only recorded for induced and c-section above

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Section 4. Secondary Outcome - All Patients

4.1.1.1.4 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Gesta_coded by method* (n(%))	Missing	1	6	7
	Sponta_vaginal_delivery_<=37 WEEKS	3 (1.4)	8 (3.6)	11 (2.5)
	Sponta_vaginal_delivery_>37 WEEKS	121 (54.5)	119 (54.1)	240 (54.3)
	LSCS in labour_<=37 WEEKS	2 (0.9)	1 (0.5)	3 (0.7)
	LSCS in labour_>37 WEEKS	32 (14.4)	24 (10.9)	56 (12.7)
	LSCS pre labour_<=37 WEEKS	7 (3.2)	8 (3.6)	15 (3.4)
	LSCS pre labour_>37 WEEKS	35 (15.8)	32 (14.5)	67 (15.2)
	Forceps/ventouse_<=37 WEEKS	1 (0.5)	1 (0.5)	2 (0.5)
	Forceps/ventouse_>37 WEEKS	17 (7.7)	20 (9.1)	37 (8.4)
	Vaginal breech_<=37 WEEKS	1 (0.5)	0	1 (0.2)
	Vaginal breech_>37 WEEKS	1 (0.5)	0	1 (0.2)
	TOP_Stillbirth_Miscarriage	2 (0.9)	7 (3.2)	9 (2.0)

N = number of patients randomised, n = number of observations

*This variable is a cross between 'Delivery Method' and 'Baby Gestational age coded'

Section 4. Secondary Outcome - All Patients

4.1.1.1.5 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Gesta_coded by labour* (n(%))	Missing	2	5	7
	Spontaneous_<=37 WEEKS	4 (1.8)	3 (1.4)	7 (1.6)
	Spontaneous_>37 WEEKS	85 (38.5)	92 (41.6)	177 (40.0)
	Induced_<=37 WEEKS	4 (1.8)	7 (3.2)	11 (2.5)
	Induced_>37 WEEKS	92 (41.6)	71 (32.1)	163 (36.9)
	C-section_<=37 WEEKS	6 (2.7)	8 (3.6)	14 (3.2)
	C-section_>37 WEEKS	28 (12.7)	33 (14.9)	61 (13.8)
	TOP_Stillbirth_Miscarriage	2 (0.9)	7 (3.2)	9 (2.0)

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N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Baby Gestational age coded'

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Section 4. Secondary Outcome - All Patients

4.1.1.1.6 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour by method* <=37 Weeks (n(%))	Spontaneous_vaginal_deliv	2 (12.5)	3 (14.3)	5 (13.5)
	Spontaneous_LSCS in labour	1 (6.3)	0	1 (2.7)
	Spontaneous_Vaginal breech	1 (6.3)	0	1 (2.7)
	Induced_vaginal_deliv	1 (6.3)	5 (23.8)	6 (16.2)
	Induced_LSCS in labour	1 (6.3)	1 (4.8)	2 (5.4)
	Induced_LSCS pre labour	1 (6.3)	0	1 (2.7)
	Induced_Forceps/ventouse	1 (6.3)	1 (4.8)	2 (5.4)
	C-section_LSCS pre labour	6 (37.5)	8 (38.1)	14 (37.8)
	TOP_Stillbirth_Miscarriage	2 (12.5)	3 (14.3)	5 (13.5)

N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Delivery Method' split by 'Baby Gestational age coded'

Section 4. Secondary Outcome - All Patients

4.1.1.1.7 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour by method* >37 Weeks (n(%))	Missing	1	1	2
	Spontaneous_vaginal_deliv	64 (31.2)	70 (35.7)	134 (33.4)
	Spontaneous_LSCS in labour	11 (5.4)	9 (4.6)	20 (5.0)
	Spontaneous_Forceps/ventouse	9 (4.4)	13 (6.6)	22 (5.5)
	Spontaneous_Vaginal breech	1 (0.5)	0	1 (0.2)
	Induced_vaginal_deliv	57 (27.8)	49 (25.0)	106 (26.4)
	Induced_LSCS in labour	21 (10.2)	15 (7.7)	36 (9.0)
	Induced_LSCS pre labour	6 (2.9)	0	6 (1.5)
	Induced_Forceps/ventouse	8 (3.9)	7 (3.6)	15 (3.7)
	C-section_LSCS pre labour	28 (13.7)	32 (16.3)	60 (15.0)
	TOP_Stillbirth_Miscarriage	0	1 (0.5)	1 (0.2)

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N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Delivery Method' split by 'Baby Gestational age coded'

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Section 4. Secondary Outcome - All Patients

4.1.1.2.1.1 Delivery Outcome

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Gestational age (Days)*	Mean	274.7	275.0	274.9
	Median	277.5	278.0	278.0
	SD	20.4	18.3	19.3
	MIN,MAX	130,298	126,297	126,298
	Q1,Q3	271,286	271,285	271,286
	n	222	218	440
	Nmiss	1	8	9
Baby Gestational age coded (n(%))*	Missing	1	8	9
	<= 24 WEEKS	2 (0.9)	2 (0.9)	4 (0.9)
	>24 and <=37 WEEKS	14 (6.3)	19 (8.7)	33 (7.5)
	>37 WEEKS	206 (92.8)	197 (90.4)	403 (91.6)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This is repeated from table 3.1 (Recorded Gestation - Visit 8 and Coded R_gestation - Visit 8)

Section 4. Secondary Outcome - All Patients

4.1.1.2.1.1 Delivery Outcome (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Gender (n(%))	NA	2	9	11
	Male	110 (49.8)	109 (50.2)	219 (50.0)
	Female	111 (50.2)	107 (49.3)	218 (49.8)
	Indeterminate	0	1 (0.5)	1 (0.2)
Birth Outcome (n(%))	NA	1	5	6
	Live Birth	218 (98.2)	213 (96.4)	431 (97.3)
	Stillbirth (intrauterine death)	0	2 (0.9)	2 (0.5)
	Miscarriage (<24 weeks)	0	4 (1.8)	4 (0.9)
	Termination of Pregnancy	2 (0.9)	1 (0.5)	3 (0.7)
	Live Birth-followed by neonatal death	2 (0.9)	1 (0.5)	3 (0.7)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - All Patients

4.1.1.2.1.2 Birth Outcome - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of Birth_Out_Ana by AllocatedTreatment*

Birth_Out_Ana(Birth Outcome categorised for analysis)	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
NA	5	1	.
Live Birth	214	220	434
TOP_Stillbirth_Miscarriage	7	2	9
Total	221	222	443

Frequency Missing = 6

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
BirthOut_itt	AllocatedTreatment METFORMIN vs PLACEBO	3.597	0.739	17.504	0.1129	0.1054

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*Analised using logistic regression (binary logit), probability modeled is Birth_Out_Ana='TOP_Stillbirth_Miscarriage'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_1_2_1_birth_outcome_analysis.lst'

Section 4. Secondary Outcome - All Patients

4.1.1.2.2.1 Delivery Outcome - birth weight

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Birth weight (g)	Mean	3449.3	3441.3	3445.4
	Median	3500.0	3500.0	3500.0
	SD	689.6	592.6	642.6
	MIN,MAX	400,4940	120,4900	120,4940
	Q1,Q3	3120,3850	3080,3780	3090,3836
	n	221	217	438
	Nmiss	2	9	11

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - All Patients

4.1.1.2.2.2 Delivery Outcome - birth weight split by gender

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight Males (g)	Mean	3530.3	3503.8	3517.1
	Median	3575.0	3500.0	3520.0
	SD	687.8	560.1	626.2
	MIN,MAX	400,4940	2230,4900	400,4940
	Q1,Q3	3240,3910	3170,3870	3180,3900
	n	110	109	219
	Nmiss	0	0	0
Birth weight Females(g)	Mean	3369.1	3408.8	3388.6
	Median	3460.0	3510.0	3465.0
	SD	685.1	535.5	615.1
	MIN,MAX	690,4550	1620,4650	690,4650
	Q1,Q3	3020,3740	3050,3700	3048,3730
	n	111	107	218
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 4. Secondary Outcome - All Patients

4.1.1.2.2.3 Delivery Outcome - birth weight split by gestation

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight <=24 WEEKS (g)	Mean	400.0	120.0	260.0
	Median	400.0	120.0	260.0
	SD	.	.	198.0
	MIN,MAX	400,400	120,120	120,400
	Q1,Q3	400,400	120,120	120,400
	n	1	1	2
	Nmiss	1	1	2
Birth weight >24 and <=37 WEEKS (g)	Mean	2102.4	2776.1	2490.2
	Median	2145.0	2730.0	2600.0
	SD	1126.5	569.2	901.2
	MIN,MAX	690,4800	1620,3740	690,4800
	Q1,Q3	1230,2750	2490,3180	2030,3110
	n	14	19	33
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - All Patients

4.1.1.2.2.3 Delivery Outcome - birth weight split by gestation (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight >37 WEEKS (g)	Mean	3555.7	3522.4	3539.4
	Median	3562.5	3530.0	3550.0
	SD	499.3	501.4	500.0
	MIN,MAX	2350,4940	2110,4900	2110,4940
	Q1,Q3	3235,3860	3160,3840	3190,3860
	n	206	197	403
	Nmiss	0	0	0

Section 4. Secondary Outcome - All Patients

4.1.1.2.2.4 Delivery Outcome - birth weight split by parity

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight parity=0 (g)	Mean	3364.9	3382.7	3374.3
	Median	3374.0	3390.0	3380.0
	SD	630.4	585.2	605.3
	MIN,MAX	690,4718	1620,4900	690,4900
	Q1,Q3	2993,3740	3000,3770	2995,3750
	n	84	94	178
	Nmiss	0	6	6
Birth weight parity=>1 (g)	Mean	3501.1	3486.1	3494.0
	Median	3610.0	3550.0	3575.0
	SD	720.9	596.6	663.8
	MIN,MAX	400,4940	120,4790	120,4940
	Q1,Q3	3240,3900	3180,3800	3190,3860
	n	137	123	260
	Nmiss	2	3	5

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 4. Secondary Outcome - All Patients

4.1.1.3 Delivery Outcome - Low birth weights

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*Gestation (days) at delivery*	*Delivery date*	*LabourType*	*Birth Outcome categorised as per CRF*	*Baby death date*	*Baby gender*	*Birth weight corrected from kg to g (g)*
11880	METFORMIN	143	30NOV2013	Induced	Miscarriage (<24 weeks)	.	NA	120
21119	PLACEBO	152	10JAN2014	Induced	Termination of Pregnancy	10JAN2014	Male	400
14264	PLACEBO	191	12JAN2013	C-section	Live Birth	.	Female	690
14270	PLACEBO	181	07MAR2013	C-section	Live Birth	.	Female	832
11786	PLACEBO	211	04NOV2013	Spontaneous	Live Birth	.	Male	1120
15028	PLACEBO	200	13JUN2013	Spontaneous	Live Birth-followed by neonatal death	17JUN2013	Male	1230
12109	PLACEBO	218	19FEB2014	C-section	Live Birth	.	Female	1250
12059	PLACEBO	234	28JUN2013	C-section	Live Birth	.	Female	1490
11420	METFORMIN	222	03AUG2012	C-section	Live Birth	.	Female	1620
11881	METFORMIN	219	04JAN2014	C-section	Live Birth	.	Female	1800

Section 4. Secondary Outcome - All Patients

4.1.1.4 Delivery Outcome - births before 24 weeks

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Gestation (days) at delivery	Delivery date	LabourType	Birth Outcome categorised as per CRF	Baby death date	Baby gender
12041	METFORMIN	126	09NOV2012	Induced	Termination of Pregnancy	.	NA
14186	METFORMIN	.	31AUG2012	Spontaneous	Miscarriage (<24 weeks)	.	NA
14302	METFORMIN	.	08MAR2013	Induced	Miscarriage (<24 weeks)	08MAR2013	Indeterminate
12086	PLACEBO	130	08SEP2013	Induced	Termination of Pregnancy	.	NA
11880	METFORMIN	143	30NOV2013	Induced	Miscarriage (<24 weeks)	.	NA
21119	PLACEBO	152	10JAN2014	Induced	Termination of Pregnancy	10JAN2014	Male

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DOI: 10.3310/eme03070

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.1 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Delivery Method(n(%))	Missing	0	1	1
	Spontaneous vaginal delivery	124 (56.4)	127 (59.6)	251 (58.0)
	LSCS in labour	34 (15.5)	25 (11.7)	59 (13.6)
	LSCS pre labour	42 (19.1)	40 (18.8)	82 (18.9)
	Forceps/ventouse	18 (8.2)	21 (9.9)	39 (9.0)
	Vaginal breech	2 (0.9)	0	2 (0.5)
C-SECTION index pregnancy(n(%))	Missing	0	1	1
	Yes	76 (34.5)	65 (30.5)	141 (32.6)
	No	144 (65.5)	148 (69.5)	292 (67.4)
Primary C-SECTION in index pregancy(n(%))	Missing	0	1	1
	Yes	46 (20.9)	42 (19.7)	88 (20.3)
	No	174 (79.1)	171 (80.3)	345 (79.7)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This is a combination between any c-section on previous pregnancies and current pregnancy c-section

Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.2 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Delivery Blood Loss (mL)	Mean	496.7	488.5	492.7
	Median	400.0	400.0	400.0
	SD	405.5	455.4	430.4
	MIN,MAX	100,2500	50,5000	50,5000
	Q1,Q3	250,600	300,600	250,600
	n	215	210	425
	Nmiss	5	4	9
Hemorrhage* (n(%))	Missing	5	4	9
	Yes	21 (9.8)	20 (9.5)	41 (9.6)
	No	194 (90.2)	190 (90.5)	384 (90.4)
SAE recorded due to Hemorrhage# (n(%))	Missing	1	1	2
	Yes	10	8	18
	No	10	11	21

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N = number of patients randomised, n = number of observations

*Hemorrhage defined as a blood loss greater than 1000ml

#Only summarised for patients with hemorrhage=yes in the item right above

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DOI: 10.3310/eme03070

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.3 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour Type (n(%))	Missing	1	0	1
	Spontaneous	89 (40.6)	95 (44.4)	184 (42.5)
	Induced	96 (43.8)	78 (36.4)	174 (40.2)
	C-section	34 (15.5)	41 (19.2)	75 (17.3)
Non Spontaneous Reason* (n(%))	Missing	1	0	1
	Post dates	24 (18.5)	16 (13.4)	40 (16.1)
	Pre-eclampsia	3 (2.3)	6 (5.0)	9 (3.6)
	Abruption	0	1 (0.8)	1 (0.4)
	Other maternal condition	45 (34.6)	46 (38.7)	91 (36.5)
	Previous C-section	20 (15.4)	16 (13.4)	36 (14.5)
	Previous obstetric history (other)	4 (3.1)	2 (1.7)	6 (2.4)
	Maternal request	10 (7.7)	5 (4.2)	15 (6.0)
	Suspected fetal compromise	12 (9.2)	13 (10.9)	25 (10.0)
	Malpresentation	5 (3.8)	8 (6.7)	13 (5.2)
	Suspected IUGR	3 (2.3)	2 (1.7)	5 (2.0)
	Suspected Macrosomia	4 (3.1)	4 (3.4)	8 (3.2)

Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.4.1 Delivery Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Gesta_coded by method* (n(%))	Missing	0	1	1
	Sponta_vaginal_delivery_<=37 WEEKS	3 (1.4)	8 (3.8)	11 (2.5)
	Sponta_vaginal_delivery_>37 WEEKS	121 (55.0)	119 (55.9)	240 (55.4)
	LSCS in labour_<=37 WEEKS	2 (0.9)	1 (0.5)	3 (0.7)
	LSCS in labour_>37 WEEKS	32 (14.5)	24 (11.3)	56 (12.9)
	LSCS pre labour_<=37 WEEKS	7 (3.2)	8 (3.8)	15 (3.5)
	LSCS pre labour_>37 WEEKS	35 (15.9)	32 (15.0)	67 (15.5)
	Forceps/ventouse_<=37 WEEKS	1 (0.5)	1 (0.5)	2 (0.5)
	Forceps/ventouse_>37 WEEKS	17 (7.7)	20 (9.4)	37 (8.5)
	Vaginal breech_<=37 WEEKS	1 (0.5)	0	1 (0.2)
	Vaginal breech_>37 WEEKS	1 (0.5)	0	1 (0.2)
Gesta_coded by labour# (n(%))	Missing	1	0	1
	Spontaneous_<=37 WEEKS	4 (1.8)	3 (1.4)	7 (1.6)
	Spontaneous_>37 WEEKS	85 (38.8)	92 (43.0)	177 (40.9)
	Induced_<=37 WEEKS	4 (1.8)	7 (3.3)	11 (2.5)
	Induced_>37 WEEKS	92 (42.0)	71 (33.2)	163 (37.6)
	C-section_<=37 WEEKS	6 (2.7)	8 (3.7)	14 (3.2)
	C-section_>37 WEEKS	28 (12.8)	33 (15.4)	61 (14.1)

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N = number of patients randomised, n = number of observations
*This variable is a cross between 'Delivery Method' and 'Baby Gestational age coded'
#This variable is a cross between 'Labour Type' and 'Baby Gestational age coded'

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DOI: 10.3310/eme03070

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.4.2 Delivery Details (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour by method* <=37 Weeks (n(%))	Spontaneous_vaginal_deliv	2 (14.3)	3 (16.7)	5 (15.6)
	Spontaneous_LSCS in labour	1 (7.1)	0	1 (3.1)
	Spontaneous_Vaginal breech	1 (7.1)	0	1 (3.1)
	Induced_vaginal_deliv	1 (7.1)	5 (27.8)	6 (18.8)
	Induced_LSCS in labour	1 (7.1)	1 (5.6)	2 (6.3)
	Induced_LSCS pre labour	1 (7.1)	0	1 (3.1)
	Induced_Forceps/ventouse	1 (7.1)	1 (5.6)	2 (6.3)
	C-section_LSCS pre labour	6 (42.9)	8 (44.4)	14 (43.8)
Labour by method* >37 Weeks (n(%))	Missing	1	1	2
	Spontaneous_vaginal_deliv	64 (31.2)	70 (35.9)	134 (33.5)
	Spontaneous_LSCS in labour	11 (5.4)	9 (4.6)	20 (5.0)
	Spontaneous_Forceps/ventouse	9 (4.4)	13 (6.7)	22 (5.5)
	Spontaneous_Vaginal breech	1 (0.5)	0	1 (0.3)
	Induced_vaginal_deliv	57 (27.8)	49 (25.1)	106 (26.5)
	Induced_LSCS in labour	21 (10.2)	15 (7.7)	36 (9.0)
	Induced_LSCS pre labour	6 (2.9)	0	6 (1.5)
	Induced_Forceps/ventouse	8 (3.9)	7 (3.6)	15 (3.8)
	C-section_LSCS pre labour	28 (13.7)	32 (16.4)	60 (15.0)

N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Delivery Method' split by 'Baby Gestational age coded'

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.4.3 Delivery Details - Preterm Birth - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of GESTA_2CODE by AllocatedTreatment

GESTA_2CODE(Gestation Code 2)	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
>24 and <=37 WEEKS	18	14	32
>37 WEEKS	196	206	402
Total	214	220	434

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
PRETERM_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.345	0.651	2.777	0.4235	0.4658

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*Analised using logistic regression (binary logit), probability modeled is PRETERM='>24 and <=37 Weeks'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_2_1_preterm_birth.lst'

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.1.1 Delivery Outcome

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth Outcome (n(%))	Live Birth	218 (99.1)	213 (99.5)	431 (99.3)
	Live Birth-followed by neonatal death	2 (0.9)	1 (0.5)	3 (0.7)
Baby Gender (n(%))	Male	109 (49.5)	109 (50.9)	218 (50.2)
	Female	111 (50.5)	105 (49.1)	216 (49.8)

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.1.2 Delivery Outcome - Birth Outcome-Neonatal Death after delivery - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of BirthOutcome by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
BirthOutcome(Birth Outcome categorised as per CRF)	*METFORMIN*	*PLACEBO*	*Total*
Live Birth	213	218	431
Live Birth-followed by neonatal death	1	2	3
Total	214	220	434

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
NEO_DEATH_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.512	0.046	5.686	0.5855	1.0000

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*Analised using logistic regression (binary logit), probability modeled is BirthOutcome='Live Birth-followed by neonatal death'

#Significance level set at p<0.05

Fisher's exact test should be used for reporting due to low cell count

Detailed analysis in file 'Empowar_11_2_Neonatal_unit.lst'

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.1.3 Delivery Outcome(Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Baby Gestational age (Days)*	Mean	275.9	276.6	276.3
	Median	278.0	278.0	278.0
	SD	15.9	11.7	14.0
	MIN,MAX	181,298	219,297	181,298
	Q1,Q3	271,286	271,285	271,286
	n	220	214	434
	Nmiss	0	0	0
Baby Gestational age coded (n(%))*	>24 and <=37 WEEKS	14 (6.4)	18 (8.4)	32 (7.4)
	>37 WEEKS	206 (93.6)	196 (91.6)	402 (92.6)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This is repeated from table 3.1 (Recorded Gestation - Visit 8 and Coded R_gestation - Visit 8)

Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.1 Delivery Outcome - birth weight

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight (g)	Mean	3463.2	3461.8	3462.5
	Median	3505.0	3510.0	3510.0
	SD	659.6	548.1	606.5
	MIN,MAX	690,4940	1620,4900	690,4940
	Q1,Q3	3130,3855	3090,3800	3110,3840
	n	220	214	434
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.2 Delivery Outcome - birth weight split by gender

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight Males (g)	Mean	3559.0	3503.8	3531.4
	Median	3580.0	3500.0	3525.0
	SD	621.2	560.1	590.7
	MIN,MAX	1120,4940	2230,4900	1120,4940
	Q1,Q3	3260,3910	3170,3870	3190,3900
	n	109	109	218
	Nmiss	0	0	0
Birth weight Females(g)	Mean	3369.1	3418.3	3393.0
	Median	3460.0	3520.0	3470.0
	SD	685.1	534.5	615.6
	MIN,MAX	690,4550	1620,4650	690,4650
	Q1,Q3	3020,3740	3080,3700	3049,3730
	n	111	105	216
	Nmiss	0	0	0

Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.3 Delivery Outcome - birth weight split by gestation

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight >24 and <=37 WEEKS (g)	Mean	2102.4	2751.9	2467.8
	Median	2145.0	2685.0	2590.0
	SD	1126.5	575.7	906.1
	MIN,MAX	690,4800	1620,3740	690,4800
	Q1,Q3	1230,2750	2490,3170	1915,3053
	n	14	18	32
	Nmiss	0	0	0
Birth weight >37 WEEKS (g)	Mean	3555.7	3527.0	3541.7
	Median	3562.5	3535.0	3550.0
	SD	499.3	498.4	498.4
	MIN,MAX	2350,4940	2110,4900	2110,4940
	Q1,Q3	3235,3860	3170,3845	3200,3860
	n	206	196	402
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.4 Delivery Outcome - birth weight split by parity

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight parity=0 (g)	Mean	3364.9	3391.0	3378.6
	Median	3374.0	3400.0	3380.0
	SD	630.4	582.8	604.2
	MIN,MAX	690,4718	1620,4900	690,4900
	Q1,Q3	2993,3740	3000,3770	3000,3750
	n	84	93	177
	Nmiss	0	0	0
Birth weight parity=>1 (g)	Mean	3523.9	3516.2	3520.3
	Median	3615.0	3560.0	3580.0
	SD	672.1	515.7	602.4
	MIN,MAX	832,4940	2110,4790	832,4940
	Q1,Q3	3240,3903	3180,3800	3200,3860
	n	136	121	257
	Nmiss	0	0	0

Section 4. Secondary Outcome - Only Alive Births

4.1.2.3 Delivery Outcome - Low birth weights

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Gestation (days) at delivery	Delivery date	LabourType	Birth Outcome categorised as per CRF	Baby death date	Baby gender	Birth weight corrected from kg to g (g)
14264	PLACEBO	191	12JAN2013	C-section	Live Birth	.	Female	690
14270	PLACEBO	181	07MAR2013	C-section	Live Birth	.	Female	832
11786	PLACEBO	211	04NOV2013	Spontaneous	Live Birth	.	Male	1120
15028	PLACEBO	200	13JUN2013	Spontaneous	Live Birth-followed by neonatal death	17JUN2013	Male	1230
12109	PLACEBO	218	19FEB2014	C-section	Live Birth	.	Female	1250
12059	PLACEBO	234	28JUN2013	C-section	Live Birth	.	Female	1490
11420	METFORMIN	222	03AUG2012	C-section	Live Birth	.	Female	1620
11881	METFORMIN	219	04JAN2014	C-section	Live Birth	.	Female	1800

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DOI: 10.3310/eme03070

EFFICACY AND MECHANISM EVALUATION 2016 VOL. 3 NO. 7

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Section 4. Outcomes - Only Alive Births

4.2.1.1 PRIMARY EFFICACY: Birth weight centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile	Mean	57.271	56.870	57.073
	Median	57.659	62.943	58.986
	SD	27.862	28.587	28.190
	MIN,MAX	0.11,99.95	0.03,99.83	0.03,99.95
	Q1,Q3	35.35,80.17	33.41,81.96	34.53,81.86
	n	220	214	434
	Nmiss	0	0	0

Section 4. Outcomes - Only Alive Births

4.2.1.2 PRIMARY EFFICACY: Birth weight centile split by gender

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile Males	Mean	57.219	55.116	56.168
	Median	58.710	56.130	57.613
	SD	28.993	29.452	29.175
	MIN,MAX	1.27,99.95	1.94,99.76	1.27,99.95
	Q1,Q3	34.15,81.92	33.26,82.48	33.26,82.48
	n	109	109	218
	Nmiss	0	0	0
Birth weight centile Females	Mean	57.323	58.690	57.987
	Median	56.465	64.308	60.840
	SD	26.837	27.684	27.197
	MIN,MAX	0.11,99.34	0.03,99.83	0.03,99.83
	Q1,Q3	35.35,79.87	38.37,81.86	36.11,81.06
	n	111	105	216
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Outcomes - Only Alive Births

4.2.1.3 PRIMARY EFFICACY: Birth weight centile split by gestation

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile >24 and <=37 WEEKS	Mean	45.277	61.655	54.490
	Median	47.213	65.106	59.095
	SD	28.994	27.900	29.113
	MIN,MAX	11.51,99.95	20.03,97.59	11.51,99.95
	Q1,Q3	14.96,67.66	33.26,86.71	27.60,78.90
	n	14	18	32
	Nmiss	0	0	0
Birth weight centile >37 WEEKS (g)	Mean	58.086	56.430	57.279
	Median	57.932	62.943	58.986
	SD	27.668	28.679	28.142
	MIN,MAX	0.11,99.89	0.03,99.83	0.03,99.89
	Q1,Q3	35.73,82.48	33.53,81.91	35.24,81.96
	n	206	196	402
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 4. Outcomes - Only Alive Births

4.2.1.4 PRIMARY EFFICACY: Birth weight centile split by parity

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile parity=0 (g)	Mean	54.271	54.718	54.506
	Median	50.234	54.451	50.563
	SD	28.134	29.603	28.834
	MIN,MAX	1.27,98.99	3.91,99.83	1.27,99.83
	Q1,Q3	32.12,79.21	30.99,81.26	31.64,80.87
	n	84	93	177
	Nmiss	0	0	0
Birth weight centile parity=>1 (g)	Mean	59.124	58.524	58.841
	Median	60.547	64.228	62.996
	SD	27.634	27.791	27.655
	MIN,MAX	0.11,99.95	0.03,99.70	0.03,99.95
	Q1,Q3	38.88,81.20	38.37,82.77	38.44,81.96
	n	136	121	257
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 4. Outcomes - Only Alive Births

4.2.2.1.1 PRIMARY EFFICACY: Birth weight centile categorised

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile (n(%))	<=3rd	3 (1.4)	3 (1.4)	6 (1.4)
	>3rd and <=5th	4 (1.8)	3 (1.4)	7 (1.6)
	>5th and <=10th	4 (1.8)	8 (3.7)	12 (2.8)
	>10th and <=90th	171 (77.7)	169 (79.0)	340 (78.3)
	>90th and <=95th	16 (7.3)	14 (6.5)	30 (6.9)
	>95th and <=97th	7 (3.2)	5 (2.3)	12 (2.8)
	>97th	15 (6.8)	12 (5.6)	27 (6.2)

Section 4. Secondary Outcome - Only Alive Births

4.2.2.1.2 PRIMARY EFFICACY: Birth weight centile categorised - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of centile_03b by AllocatedTreatment*

	AllocatedTreatment(Allocated Treatment)		
centile_03b	*METFORMIN*	*PLACEBO*	*Total*
No	211	217	428
Yes	3	3	6
Total	214	220	434

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
centile_03b_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.028	0.205	5.152	0.9728	1.0000

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26

By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is centile_03b='Yes'

#Significance level set at p<0.05

Fisher's exact test should be used for reporting due to low cell count

Detailed analysis in file 'Empowar_4_2_2_1_weight_centile.lst'

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Section 4. Secondary Outcome - Only Alive Births

4.2.2.1.3 PRIMARY EFFICACY: Birth weight centile categorised - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of centile_10b by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
centile_10b	*METFORMIN*	*PLACEBO*	*Total*
No	200	209	409
Yes	14	11	25
Total	214	220	434

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
centile_10b_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.330	0.590	2.999	0.4918	0.5408

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26

*Analised using logistic regression (binary logit), probability modeled is centile_10b='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_2_2_1_weight_centile.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 4. Outcomes - Only Alive Births

4.2.2.2 PRIMARY EFFICACY: Birth weight centile categorised split by gender

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile Males(n(%))	<=3rd	2 (1.8)	2 (1.8)	4 (1.8)
	>3rd and <=5th	2 (1.8)	3 (2.8)	5 (2.3)
	>5th and <=10th	3 (2.8)	4 (3.7)	7 (3.2)
	>10th and <=90th	81 (74.3)	86 (78.9)	167 (76.6)
	>90th and <=95th	8 (7.3)	6 (5.5)	14 (6.4)
	>95th and <=97th	5 (4.6)	4 (3.7)	9 (4.1)
	>97th	8 (7.3)	4 (3.7)	12 (5.5)
Split Birth weight Centile Females(n(%))	<=3rd	1 (0.9)	1 (1.0)	2 (0.9)
	>3rd and <=5th	2 (1.8)	0	2 (0.9)
	>5th and <=10th	1 (0.9)	4 (3.8)	5 (2.3)
	>10th and <=90th	90 (81.1)	83 (79.0)	173 (80.1)
	>90th and <=95th	8 (7.2)	8 (7.6)	16 (7.4)
	>95th and <=97th	2 (1.8)	1 (1.0)	3 (1.4)
	>97th	7 (6.3)	8 (7.6)	15 (6.9)

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DOI: 10.3310/eme03070

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Section 4. Outcomes - Only Alive Births

4.2.2.3 PRIMARY EFFICACY: Birth weight centile categorised split by gestation

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile >24 and <=37 WEEKS(n(%))	>10th and <=90th	13 (92.9)	14 (77.8)	27 (84.4)
	>90th and <=95th	0	1 (5.6)	1 (3.1)
	>95th and <=97th	0	1 (5.6)	1 (3.1)
	>97th	1 (7.1)	2 (11.1)	3 (9.4)
Split Birth weight Centile >37 WEEKS(n(%))	<=3rd	3 (1.5)	3 (1.5)	6 (1.5)
	>3rd and <=5th	4 (1.9)	3 (1.5)	7 (1.7)
	>5th and <=10th	4 (1.9)	8 (4.1)	12 (3.0)
	>10th and <=90th	158 (76.7)	155 (79.1)	313 (77.9)
	>90th and <=95th	16 (7.8)	13 (6.6)	29 (7.2)
	>95th and <=97th	7 (3.4)	4 (2.0)	11 (2.7)
	>97th	14 (6.8)	10 (5.1)	24 (6.0)

Section 4. Outcomes - Only Alive Births

4.2.2.4 PRIMARY EFFICACY: Birth weight centile categorised split by parity

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile parity=0 (n(%))	<=3rd	1 (1.2)	0	1 (0.6)
	>3rd and <=5th	2 (2.4)	3 (3.2)	5 (2.8)
	>5th and <=10th	1 (1.2)	5 (5.4)	6 (3.4)
	>10th and <=90th	67 (79.8)	72 (77.4)	139 (78.5)
	>90th and <=95th	5 (6.0)	7 (7.5)	12 (6.8)
	>95th and <=97th	4 (4.8)	1 (1.1)	5 (2.8)
	>97th	4 (4.8)	5 (5.4)	9 (5.1)
Split Birth weight Centile parity=>1 (n(%))	<=3rd	2 (1.5)	3 (2.5)	5 (1.9)
	>3rd and <=5th	2 (1.5)	0	2 (0.8)
	>5th and <=10th	3 (2.2)	3 (2.5)	6 (2.3)
	>10th and <=90th	104 (76.5)	97 (80.2)	201 (78.2)
	>90th and <=95th	11 (8.1)	7 (5.8)	18 (7.0)
	>95th and <=97th	3 (2.2)	4 (3.3)	7 (2.7)
	>97th	11 (8.1)	7 (5.8)	18 (7.0)

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Section 4. Outcomes - Only Alive Births

4.3.1 PRIMARY EFFICACY: Calculated Z score

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Z-score for birth weight centile	Mean	0.2680	0.2464	0.2573
	Median	0.1932	0.3304	0.2272
	SD	1.0055	1.0179	1.0105
	MIN,MAX	-3.071,3.299	-3.428,2.929	-3.428,3.299
	Q1,Q3	-0.376,0.848	-0.429,0.914	-0.398,0.910
	n	220	214	434
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 4. Outcomes - Only Alive Births

4.3.2 PRIMARY EFFICACY: Calculated Z score - Statistical Analysis

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
z-score - itt	0.358	0.1267	220	0.329	0.1231	214	-0.029	-0.217	0.158	0.094	0.7597

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 4.3.1 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means for the z score by allocated treatment,
SE represents standard error of the estimated mean and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_4_3_2_primary_outcome_z_analysis.lst'
Parameter shown normal behavior

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.1 Fasted Glucose - Visit 3 Randomisation (12-16 Weeks)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
GTT - V3 - base (mmol/L)	Mean	4.39	4.41	4.40
	Median	4.40	4.40	4.40
	SD	0.34	0.40	0.37
	MIN,MAX	3.5,5.6	3.1,5.6	3.1,5.6
	Q1,Q3	4.2,4.6	4.1,4.7	4.1,4.6
	n	223	226	449
	Nmiss	0	0	0
GTT - V3 - 2 hr (mmol/L)	Mean	5.50	5.20	5.35
	Median	5.40	5.20	5.30
	SD	1.09	1.08	1.10
	MIN,MAX	2.4,7.8	1.7,7.7	1.7,7.8
	Q1,Q3	4.8,6.3	4.6,6.0	4.7,6.1
	n	223	226	449
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*If baseline (fasting) sample >5.5 mmol/L or 2 hr sample >7.8 mmol then the subject is not eligible to continue in the study

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.2 Fasted Glucose - Visit 5 (28 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
GTT - V5 - base (mmol/L)	Mean	4.49	4.38	4.44
	Median	4.40	4.40	4.40
	SD	0.47	0.41	0.44
	MIN,MAX	2.9,5.6	3.4,6.0	2.9,6.0
	Q1,Q3	4.2,4.8	4.1,4.7	4.1,4.7
	n	184	175	359
	Nmiss	39	51	90
GTT - V5 - 2 hr (mmol/L)	Mean	5.85	5.58	5.72
	Median	5.80	5.50	5.60
	SD	1.20	1.32	1.27
	MIN,MAX	2.4,8.9	3.0,12.3	2.4,12.3
	Q1,Q3	5.0,6.7	4.8,6.0	4.9,6.4
	n	184	174	358
	Nmiss	39	52	91

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.3 Fasted Glucose - Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
GTT - V6 - base (mmol/L)	Mean	4.42	4.35	4.39
	Median	4.30	4.30	4.30
	SD	0.48	0.45	0.47
	MIN,MAX	2.7,5.8	3.4,5.9	2.7,5.9
	Q1,Q3	4.0,4.7	4.0,4.6	4.0,4.7
	n	151	143	294
	Nmiss	72	83	155
GTT - V6 - 2 hr (mmol/L)	Mean	5.96	5.70	5.83
	Median	5.70	5.70	5.70
	SD	1.46	1.32	1.40
	MIN,MAX	3.0,10.3	2.7,9.1	2.7,10.3
	Q1,Q3	4.9,6.9	4.8,6.4	4.9,6.7
	n	148	142	290
	Nmiss	75	84	159

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.4.1 Fasted Glucose - Visit 6 (36 Weeks) - Statistical Analysis

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Glucose_V6_Baseline - itt	4.420	0.0660	151	4.360	0.0624	143	-0.060	-0.163	0.043	1.330	0.2498
Glucose_V6_Two_Hour - itt	6.083	0.2001	148	5.832	0.1890	142	-0.251	-0.565	0.062	2.487	0.1159

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 5.1.3 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means for the glucose in blood by allocated treatment,
SE represents standard error of the estimated mean and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_1_4_glucose_outcome_analysis.lst'
Parameters shown normal or near-normal behavior

DOI: 10.3310/eme03070

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.4.2 Fasted Glucose - Visit 5 (28 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Glucose_V5_Baseline - itt	4.468	0.0599	184	4.363	0.0570	175	-0.105	-0.193	-0.016	5.383	0.0209
Glucose_V5_Two_Hour - itt	5.787	0.1716	184	5.537	0.1633	174	-0.250	-0.504	0.005	3.724	0.0545

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 5.1.2 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means for the glucose in blood by allocated treatment,
SE represents standard error of the estimated mean and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_1_4_glucose_outcome_analysis_v5.lst'
Parameters shown normal or near-normal behavior

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.1 Fasted Glucose - Visit 5 (28 Weeks) split by C-section

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - GTT - V5 - base (mmol/L)	Mean	4.56	4.46	4.51
	Median	4.55	4.40	4.50
	SD	0.51	0.44	0.48
	MIN,MAX	3.6,5.6	3.5,6.0	3.5,6.0
	Q1,Q3	4.2,5.0	4.2,4.8	4.2,4.8
	n	64	52	116
	Nmiss	6	9	15
Yes C-section - GTT - V5 - 2 hr (mmol/L)	Mean	6.10	5.86	5.99
	Median	6.00	5.60	5.85
	SD	1.44	1.41	1.42
	MIN,MAX	2.4,8.9	4.2,12.3	2.4,12.3
	Q1,Q3	5.2,7.4	5.1,6.3	5.1,7.0
	n	64	52	116
	Nmiss	6	9	15

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.1 Fasted Glucose - Visit 5 (28 Weeks) split by C-section

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
No C-section - GTT - V5 - base (mmol/L)	Mean	4.45	4.35	4.40
	Median	4.40	4.30	4.40
	SD	0.44	0.40	0.42
	MIN,MAX	2.9,5.6	3.4,5.6	2.9,5.6
	Q1,Q3	4.2,4.7	4.1,4.6	4.1,4.7
	n	120	122	242
	Nmiss	21	21	42
No C-section - GTT - V5 - 2 hr (mmol/L)	Mean	5.71	5.47	5.59
	Median	5.70	5.50	5.60
	SD	1.03	1.27	1.16
	MIN,MAX	3.0,8.7	3.0,10.0	3.0,10.0
	Q1,Q3	4.9,6.4	4.6,6.0	4.9,6.3
	n	120	121	241
	Nmiss	21	22	43

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.2 Fasted Glucose - Visit 6 (36 Weeks) split by C-section

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - GTT - V6 - base (mmol/L)	Mean	4.43	4.39	4.41
	Median	4.50	4.30	4.30
	SD	0.50	0.47	0.49
	MIN,MAX	2.7,5.6	3.6,5.5	2.7,5.6
	Q1,Q3	4.1,4.8	4.0,4.7	4.0,4.7
	n	52	43	95
	Nmiss	17	16	33
Yes C-section - GTT - V6 - 2 hr (mmol/L	Mean	6.18	5.79	6.00
	Median	6.10	5.80	6.00
	SD	1.58	1.20	1.43
	MIN,MAX	3.0,10.3	2.7,8.5	2.7,10.3
	Q1,Q3	4.9,7.4	5.0,6.6	5.0,6.9
	n	52	43	95
	Nmiss	17	16	33

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.2 Fasted Glucose - Visit 6 (36 Weeks) split by C-section

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
No C-section - GTT - V6 - base (mmol/L)	Mean	4.41	4.34	4.37
	Median	4.30	4.30	4.30
	SD	0.47	0.45	0.46
	MIN,MAX	3.4,5.8	3.4,5.9	3.4,5.9
	Q1,Q3	4.0,4.7	4.0,4.6	4.0,4.6
	n	99	100	199
	Nmiss	40	40	80
No C-section - GTT - V6 - 2 hr (mmol/L)	Mean	5.84	5.65	5.75
	Median	5.55	5.40	5.50
	SD	1.38	1.38	1.38
	MIN,MAX	3.5,9.8	3.2,9.1	3.2,9.8
	Q1,Q3	4.9,6.8	4.7,6.3	4.8,6.5
	n	96	99	195
	Nmiss	43	41	84

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_GTT_V5_base (mmol/L)	Mean	4.03	4.13	4.08
	Median	4.00	4.20	4.10
	SD	0.25	0.12	0.18
	MIN,MAX	3.8,4.3	4.0,4.2	3.8,4.3
	Q1,Q3	3.8,4.3	4.0,4.2	4.0,4.2
	n	3	3	6
	Nmiss	0	0	0
3%<=_GTT_V5_2 hr (mmol/L)	Mean	4.60	6.13	5.37
	Median	4.80	5.70	4.95
	SD	0.35	1.31	1.20
	MIN,MAX	4.2,4.8	5.1,7.6	4.2,7.6
	Q1,Q3	4.2,4.8	5.1,7.6	4.8,5.7
	n	3	3	6
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
5%<=_GTT_V5_base (mmol/L)	Mean	4.04	4.08	4.06
	Median	4.00	4.15	4.10
	SD	0.18	0.27	0.22
	MIN,MAX	3.8,4.3	3.6,4.4	3.6,4.4
	Q1,Q3	4.0,4.1	4.0,4.2	4.0,4.2
	n	5	6	11
	Nmiss	1	0	1
5%<=_GTT_V5_2 hr (mmol/L)	Mean	4.24	5.18	4.75
	Median	4.80	5.40	4.80
	SD	1.07	1.63	1.43
	MIN,MAX	2.4,5.0	3.0,7.6	2.4,7.6
	Q1,Q3	4.2,4.8	3.8,5.9	3.8,5.7
	n	5	6	11
	Nmiss	1	0	1

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_GTT_V5_base (mmol/L)	Mean	4.30	4.22	4.25
	Median	4.20	4.20	4.20
	SD	0.42	0.30	0.34
	MIN,MAX	3.8,5.0	3.6,4.7	3.6,5.0
	Q1,Q3	4.0,4.6	4.0,4.4	4.0,4.4
	n	8	11	19
	Nmiss	2	2	4
10%<=_GTT_V5_2 hr (mmol/L)	Mean	4.60	4.91	4.78
	Median	4.80	5.10	4.80
	SD	1.09	1.37	1.23
	MIN,MAX	2.4,6.2	3.0,7.6	2.4,7.6
	Q1,Q3	4.2,5.1	3.7,5.9	3.8,5.7
	n	8	11	19
	Nmiss	2	2	4

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%> AND 90%<=_GTT_V5_base (mmol/L)	Mean	4.47	4.37	4.42
	Median	4.40	4.35	4.40
	SD	0.46	0.41	0.44
	MIN,MAX	2.9,5.5	3.4,6.0	2.9,6.0
	Q1,Q3	4.2,4.8	4.1,4.6	4.2,4.7
	n	142	134	276
	Nmiss	21	25	46
10%> AND 90%<=_GTT_V5_2 hr (mmol/L)	Mean	5.85	5.61	5.73
	Median	5.85	5.50	5.70
	SD	1.20	1.30	1.25
	MIN,MAX	3.0,8.9	3.1,12.3	3.0,12.3
	Q1,Q3	4.9,6.7	4.9,6.1	4.9,6.5
	n	142	133	275
	Nmiss	21	26	47

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_GTT_V5_base (mmol/L)	Mean	4.60	4.51	4.56
	Median	4.60	4.40	4.60
	SD	0.50	0.43	0.47
	MIN,MAX	3.7,5.6	3.7,5.6	3.7,5.6
	Q1,Q3	4.3,4.9	4.3,4.7	4.3,4.8
	n	34	29	63
	Nmiss	2	2	4
90%>_GTT_V5_2 hr (mmol/L)	Mean	6.14	5.75	5.96
	Median	5.90	5.40	5.70
	SD	1.08	1.36	1.22
	MIN,MAX	4.4,8.3	3.6,9.8	3.6,9.8
	Q1,Q3	5.3,7.1	5.0,6.0	5.1,6.5
	n	34	29	63
	Nmiss	2	2	4

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
95%>_GTT_V5_base (mmol/L)	Mean	4.71	4.50	4.61
	Median	4.60	4.45	4.60
	SD	0.51	0.37	0.45
	MIN,MAX	4.0,5.6	4.0,5.5	4.0,5.6
	Q1,Q3	4.3,5.2	4.3,4.7	4.3,4.8
	n	19	16	35
	Nmiss	1	2	3
95%>_GTT_V5_2 hr (mmol/L)	Mean	6.11	5.75	5.95
	Median	5.90	5.35	5.90
	SD	1.03	1.51	1.27
	MIN,MAX	4.4,8.3	3.6,9.8	3.6,9.8
	Q1,Q3	5.3,7.0	5.0,6.1	5.2,6.4
	n	19	16	35
	Nmiss	1	2	3

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_GTT_V5_base (mmol/L)	Mean	4.78	4.49	4.64
	Median	4.70	4.30	4.60
	SD	0.45	0.43	0.46
	MIN,MAX	4.1,5.6	4.0,5.5	4.0,5.6
	Q1,Q3	4.5,5.2	4.2,4.7	4.3,4.9
	n	12	11	23
	Nmiss	1	2	3
97%>_GTT_V5_2 hr (mmol/L)	Mean	5.88	5.78	5.83
	Median	5.80	5.90	5.90
	SD	0.82	1.58	1.21
	MIN,MAX	4.8,7.5	3.6,9.8	3.6,9.8
	Q1,Q3	5.3,6.4	5.0,6.1	5.2,6.3
	n	12	11	23
	Nmiss	1	2	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_GTT_V6_base (mmol/L)	Mean	3.90	.	3.90
	Median	3.50	.	3.50
	SD	0.78	.	0.78
	MIN,MAX	3.4,4.8	.,.	3.4,4.8
	Q1,Q3	3.4,4.8	.,.	3.4,4.8
	n	3	0	3
	Nmiss	0	3	3
3%<=_GTT_V6_2 hr (mmol/L)	Mean	5.17	.	5.17
	Median	4.50	.	4.50
	SD	1.99	.	1.99
	MIN,MAX	3.6,7.4	.,.	3.6,7.4
	Q1,Q3	3.6,7.4	.,.	3.6,7.4
	n	3	0	3
	Nmiss	0	3	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
5%<=_GTT_V6_base (mmol/L)	Mean	3.90	3.90	3.90
	Median	3.90	3.90	3.90
	SD	0.55	0.30	0.45
	MIN,MAX	3.4,4.8	3.6,4.2	3.4,4.8
	Q1,Q3	3.5,3.9	3.6,4.2	3.6,4.1
	n	5	3	8
	Nmiss	1	3	4
5%<=_GTT_V6_2 hr (mmol/L)	Mean	4.80	4.90	4.84
	Median	4.50	4.60	4.55
	SD	1.73	1.18	1.45
	MIN,MAX	3.0,7.4	3.9,6.2	3.0,7.4
	Q1,Q3	3.6,5.5	3.9,6.2	3.8,5.9
	n	5	3	8
	Nmiss	1	3	4

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_GTT_V6_base (mmol/L)	Mean	4.14	4.41	4.28
	Median	4.10	4.50	4.35
	SD	0.54	0.49	0.52
	MIN,MAX	3.4,4.8	3.6,5.1	3.4,5.1
	Q1,Q3	3.7,4.7	4.1,4.8	3.9,4.7
	n	8	8	16
	Nmiss	2	5	7
10%<=_GTT_V6_2 hr (mmol/L)	Mean	5.45	5.26	5.36
	Median	5.65	5.55	5.65
	SD	1.71	1.48	1.55
	MIN,MAX	3.0,7.9	2.7,7.3	2.7,7.9
	Q1,Q3	4.1,6.7	4.3,6.3	4.2,6.3
	n	8	8	16
	Nmiss	2	5	7

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%> AND 90%<=_GTT_V6_base (mmol/L)	Mean	4.39	4.33	4.36
	Median	4.30	4.20	4.30
	SD	0.46	0.45	0.46
	MIN,MAX	2.7,5.8	3.4,5.9	2.7,5.9
	Q1,Q3	4.0,4.7	4.0,4.6	4.0,4.6
	n	116	111	227
	Nmiss	44	45	89
10%> AND 90%<=_GTT_V6_2 hr (mmol/L)	Mean	5.83	5.73	5.78
	Median	5.70	5.70	5.70
	SD	1.38	1.38	1.38
	MIN,MAX	3.2,9.5	3.2,9.1	3.2,9.5
	Q1,Q3	4.7,6.8	4.7,6.5	4.7,6.6
	n	113	111	224
	Nmiss	47	45	92

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_GTT_V6_base (mmol/L)	Mean	4.63	4.45	4.55
	Median	4.60	4.35	4.40
	SD	0.49	0.46	0.48
	MIN,MAX	3.8,5.6	3.9,5.5	3.8,5.6
	Q1,Q3	4.3,5.0	4.1,4.6	4.2,4.8
	n	27	24	51
	Nmiss	9	5	14
90%>_GTT_V6_2 hr (mmol/L)	Mean	6.67	5.70	6.22
	Median	6.50	5.70	5.90
	SD	1.55	0.98	1.39
	MIN,MAX	3.9,10.3	3.6,8.3	3.6,10.3
	Q1,Q3	5.5,7.5	5.0,6.2	5.2,7.2
	n	27	23	50
	Nmiss	9	6	15

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
95%>_GTT_V6_base (mmol/L)	Mean	4.79	4.28	4.54
	Median	4.70	4.30	4.40
	SD	0.49	0.31	0.48
	MIN,MAX	4.0,5.6	3.9,5.1	3.9,5.6
	Q1,Q3	4.4,5.1	4.0,4.4	4.2,4.8
	n	14	13	27
	Nmiss	6	3	9
95%>_GTT_V6_2 hr (mmol/L)	Mean	6.52	5.63	6.11
	Median	6.30	5.55	5.85
	SD	1.52	0.82	1.30
	MIN,MAX	3.9,9.8	4.5,7.2	3.9,9.8
	Q1,Q3	5.5,7.5	5.0,6.0	5.1,7.2
	n	14	12	26
	Nmiss	6	4	10

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_GTT_V6_base (mmol/L)	Mean	4.93	4.28	4.58
	Median	4.85	4.30	4.40
	SD	0.40	0.35	0.49
	MIN,MAX	4.4,5.6	3.9,5.1	3.9,5.6
	Q1,Q3	4.7,5.2	4.0,4.3	4.3,5.0
	n	8	9	17
	Nmiss	5	2	7
97%>_GTT_V6_2 hr (mmol/L)	Mean	6.90	5.60	6.25
	Median	6.65	5.15	5.70
	SD	1.63	0.98	1.46
	MIN,MAX	5.2,9.8	4.5,7.2	4.5,9.8
	Q1,Q3	5.6,7.9	5.0,6.4	5.1,7.4
	n	8	8	16
	Nmiss	5	3	8

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.1 Gestational diabetes mellitus (GDM) - OGTT Test*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
GDM WHO CRITERIA*# (n(%))	Missing	73	83	156
	No	124 (82.7)	124 (86.7)	248 (84.6)
	Yes	26 (17.3)	19 (13.3)	45 (15.4)
GDM WHO CRITERIA CODED# (n(%))	Missing	73	83	156
	GDM first at visit 5 (28 weeks)	12 (8.0)	10 (7.0)	22 (7.5)
	GDM first at visit 6 (36 weeks)	14 (9.3)	9 (6.3)	23 (7.8)
	NO GDM	124 (82.7)	124 (86.7)	248 (84.6)
GDM IADPSG CRITERIA*$ (n(%))	Missing	70	84	154
	No	117 (76.5)	116 (81.7)	233 (79.0)
	Yes	36 (23.5)	26 (18.3)	62 (21.0)
GDM IADPSG CRITERIA CODED$ (n(%))	Missing	70	84	154
	GDM first at visit 5 (28 weeks)	26 (17.0)	11 (7.7)	37 (12.5)
	GDM first at visit 6 (36 weeks)	10 (6.5)	15 (10.6)	25 (8.5)
	NO GDM	117 (76.5)	116 (81.7)	233 (79.0)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Once GDM is present in visit 5 then it will stay present in visit 6
#WHO criteria: Fasting glucose >= 7.0 mmol/l or 2hr glucose >=7.8 mmol/l
$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.2 Gestational diabetes mellitus (GDM) IADPSG$ - OGTT Test*- Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of GDM_IAD by AllocatedTreatment*

GDM_IAD(GDM calculated using IADPSG criteria (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Missing	84	70	.
No	116	117	233
Yes	26	36	62
Total	142	153	295

Frequency Missing = 154

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
GDMIAD_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.728	0.414	1.283	0.2726	0.3174

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Summary statistics are presented in table 5.1.6.1 of this report

*Analised using logistic regression (binary logit), probability modeled GDM_IAD='Yes'

#Significance level set at p<0.05. Detailed analysis in file 'Empowar_5_1_6_glucose_GDM_analysis.lst'

$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.3 Gestational diabetes mellitus (GDM) IADPSG$ - OGTT Test*- Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of GDM_CODE_IAD by AllocatedTreatment

GDM_CODE_IAD(GDM calculated using IADPSG criteria by visit)	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Missing	84	70	.
GDM first at visit 5 (28 weeks)	11	26	37
GDM first at visit 6 (36 weeks)	15	10	25
NO GDM	116	117	233
Total	142	153	295

Frequency Missing = 154

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Summary statistics are presented in table 5.1.6.1 of this report
*Analised using The Mantel-Haenszel chi-square statistic tests
#Significance level set at p<0.05. Detailed analysis in file 'Empowar_5_1_6_glucose_GDM_analysis.lst'
$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.3 Gestational diabetes mellitus (GDM) IADPSG$ - OGTT Test*- Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Statistics for Table of GDM_CODE_IAD by AllocatedTreatment

Statistic	*DF*	*Value*	*Prob*
Chi-Square	2	6.6845	0.0354
Likelihood Ratio Chi-Square	2	6.8605	0.0324
Mantel-Haenszel Chi-Square	1	3.2419	0.0718
Phi Coefficient		0.1505	
Contingency Coefficient		0.1489	
Cramer's V		0.1505	

Effective Sample Size = 295
Frequency Missing = 154

WARNING: 34 % of the data are missing.

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Summary statistics are presented in table 5.1.6.1 of this report
*Analised using The Mantel-Haenszel chi-square statistic tests
#Significance level set at p<0.05. Detailed analysis in file 'Empowar_5_1_6_glucose_GDM_analysis.lst'
$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

By: Aryelly Rodriguez - ECTU Statistician

Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.1 Insulin - Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Insulin - Visit 2 (mIU/ml)	Mean	22.077	21.953	22.015
	Median	19.457	19.765	19.679
	SD	10.201	12.264	11.262
	MIN,MAX	3.73,71.22	2.00,106.02	2.00,106.02
	Q1,Q3	15.51,26.41	14.93,26.72	15.26,26.60
	n	189	188	377
	Nmiss	34	38	72
Insulin - Visit 5 (mIU/ml)	Mean	27.487	26.313	26.920
	Median	25.015	23.158	24.014
	SD	14.282	19.053	16.740
	MIN,MAX	6.86,121.29	6.82,196.84	6.82,196.84
	Q1,Q3	19.46,31.33	17.18,30.29	17.99,30.73
	n	154	144	298
	Nmiss	69	82	151

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.1 Insulin - Visit 6 (36 Weeks) (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Insulin - Visit 6 (mIU/ml)	Mean	30.086	32.794	31.419
	Median	27.342	27.088	27.222
	SD	13.123	24.547	19.605
	MIN,MAX	6.46,91.87	9.78,204.26	6.46,204.26
	Q1,Q3	20.91,35.86	20.36,36.61	20.73,35.86
	n	131	127	258
	Nmiss	92	99	191

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.2.1 Fasted Insulin - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Insulin_log_visit_6 - itt	3.438	0.0759	131	3.442	0.0724	127	0.005	-0.104	0.113	0.007	0.9342

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Summary statistics are presented in table 5.2.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed insulin in blood by allocated treatment,
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log transformed mean and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_2_2_INSULIN_RES_outcome_analysis.lst'
Parameter shown normal or near-normal behavior

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.2.2 Fasted Insulin - Visit 5 (28 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Insulin_log_visit_5 - itt	3.305	0.0694	154	3.214	0.0656	144	-0.091	-0.189	0.007	3.374	0.0673

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Summary statistics are presented in table 5.2.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed insulin in blood by allocated treatment,
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log transformed mean and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_2_2_INSULIN_RES_outcome_analysis_v5'.lst
Parameter shown normal or near-normal behavior

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.1 HOMA-IR - Visit 2 Consent/Baseline (10-16 Weeks) and Visit 5 (28 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
HOMA - visit 2 - base	Mean	4.360	4.363	4.362
	Median	3.855	3.903	3.857
	SD	2.157	2.755	2.470
	MIN,MAX	0.71,14.24	0.34,24.02	0.34,24.02
	Q1,Q3	2.94,5.16	2.74,5.16	2.88,5.16
	n	189	188	377
	Nmiss	34	38	72
HOMA - visit 5 - base	Mean	5.563	5.234	5.404
	Median	4.862	4.651	4.735
	SD	3.298	4.173	3.745
	MIN,MAX	1.10,28.57	1.23,41.12	1.10,41.12
	Q1,Q3	3.72,6.46	3.21,6.13	3.31,6.28
	n	153	144	297
	Nmiss	70	82	152

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.2 HOMA-IR - Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
HOMA - visit 6 - base	Mean	5.978	6.298	6.133
	Median	5.345	5.056	5.175
	SD	2.888	4.777	3.914
	MIN,MAX	1.15,16.74	1.73,34.50	1.15,34.50
	Q1,Q3	4.04,7.18	3.72,7.26	3.87,7.18
	n	131	123	254
	Nmiss	92	103	195

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.3.1 HOMA_IR - VISIT 6 (36 WEEKS) - Statistical Analysis

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
HOMA-IR_log_visit_6 - itt	1.808	0.0825	131	1.782	0.0787	123	-0.026	-0.145	0.093	0.187	0.6656

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Summary statistics are presented in table 5.3.2 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed HOMA-IR in blood by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_3_4_glucose_outcome_analysis.lst'
Parameter shown normal or near-normal behavior

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.3.2 HOMA_IR - VISIT 5 (28 WEEKS) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
HOMA-IR_log_visit_5 - itt	1.673	0.0774	153	1.563	0.0731	144	-0.111	-0.220	-0.002	3.984	0.0469

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Summary statistics are presented in table 5.3.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed HOMA-IR in blood by allocated treatment,
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_3_4_glucose_outcome_analysis_5v.lst'
Parameter shown normal or near-normal behavior

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.1 HOMA-IR - Visit 5 (28 Weeks) split by C-section

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - HOMA_IR - V5 - base	Mean	6.22	6.03	6.13
	Median	5.38	5.31	5.33
	SD	4.07	4.04	4.04
	MIN,MAX	1.6,28.6	1.8,23.1	1.6,28.6
	Q1,Q3	3.8,7.3	3.5,6.8	3.8,7.0
	n	50	46	96
	Nmiss	20	15	35
No C-section - HOMA_IR - V5 - base	Mean	5.25	4.86	5.06
	Median	4.69	4.25	4.51
	SD	2.82	4.22	3.56
	MIN,MAX	1.1,19.0	1.2,41.1	1.1,41.1
	Q1,Q3	3.4,6.1	3.1,5.7	3.2,5.8
	n	103	97	200
	Nmiss	38	46	84

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.2 HOMA-IR - Visit 6 (36 Weeks) split by C-section

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - HOMA_IR - V6 - base	Mean	6.52	5.74	6.17
	Median	5.88	5.20	5.46
	SD	3.06	2.79	2.95
	MIN,MAX	1.1,13.8	1.7,16.2	1.1,16.2
	Q1,Q3	4.4,7.8	3.9,7.2	4.2,7.2
	n	46	38	84
	Nmiss	23	21	44
No C-section - HOMA_IR - V6 - base	Mean	5.68	6.55	6.11
	Median	5.15	4.99	5.07
	SD	2.76	5.43	4.32
	MIN,MAX	1.6,16.7	1.7,34.5	1.6,34.5
	Q1,Q3	3.7,6.6	3.7,7.4	3.7,7.0
	n	85	85	170
	Nmiss	54	55	109

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_HOMA_IR_V5_base	Mean	3.55	4.30	3.85
	Median	4.04	4.30	4.04
	SD	1.73	2.77	1.90
	MIN,MAX	1.6,5.0	2.3,6.3	1.6,6.3
	Q1,Q3	1.6,5.0	2.3,6.3	2.3,5.0
	n	3	2	5
	Nmiss	0	1	1
5%<=_HOMA_IR_V5_base	Mean	3.63	3.41	3.52
	Median	4.04	2.83	3.14
	SD	1.39	1.68	1.46
	MIN,MAX	1.6,5.0	2.1,6.3	1.6,6.3
	Q1,Q3	2.8,4.7	2.3,3.5	2.3,4.7
	n	5	5	10
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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DOI: 10.3310/eme03070

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_HOMA_IR_V5_base	Mean	4.37	8.21	6.40
	Median	4.81	3.46	4.69
	SD	1.52	12.46	9.08
	MIN,MAX	1.6,6.5	2.1,41.1	1.6,41.1
	Q1,Q3	3.4,5.2	2.8,6.3	2.8,5.5
	n	8	9	17
	Nmiss	2	4	6
10%> AND 90%<=_HOMA_IR_V5_base	Mean	5.30	4.96	5.13
	Median	4.59	4.64	4.63
	SD	2.73	2.82	2.78
	MIN,MAX	1.1,19.0	1.2,23.1	1.1,23.1
	Q1,Q3	3.5,6.4	3.2,5.7	3.3,6.2
	n	117	109	226
	Nmiss	46	50	96

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_HOMA_IR_V5_base	Mean	7.00	5.39	6.24
	Median	5.74	4.75	5.51
	SD	5.06	3.54	4.44
	MIN,MAX	2.7,28.6	1.5,19.4	1.5,28.6
	Q1,Q3	4.6,7.1	2.9,6.9	4.3,6.9
	n	28	25	53
	Nmiss	8	6	14
95%>_HOMA_IR_V5_base	Mean	7.10	5.34	6.16
	Median	5.79	4.50	5.53
	SD	6.34	4.18	5.28
	MIN,MAX	2.7,28.6	1.5,19.4	1.5,28.6
	Q1,Q3	4.5,6.6	2.6,6.6	3.3,6.6
	n	14	16	30
	Nmiss	6	2	8

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_HOMA_IR_V5_base	Mean	8.32	5.61	6.83
	Median	5.95	4.48	5.73
	SD	7.71	4.93	6.30
	MIN,MAX	3.1,28.6	1.5,19.4	1.5,28.6
	Q1,Q3	5.7,6.6	2.5,6.9	3.7,6.7
	n	9	11	20
	Nmiss	4	2	6

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_HOMA_IR_V6_base	Mean	2.99	.	2.99
	Median	2.23	.	2.23
	SD	1.39	.	1.39
	MIN,MAX	2.1,4.6	.,.	2.1,4.6
	Q1,Q3	2.1,4.6	.,.	2.1,4.6
	n	3	0	3
	Nmiss	0	3	3
5%<=_HOMA_IR_V6_base	Mean	3.21	3.86	3.45
	Median	3.51	4.29	3.54
	SD	1.03	0.76	0.94
	MIN,MAX	2.1,4.6	3.0,4.3	2.1,4.6
	Q1,Q3	2.2,3.6	3.0,4.3	2.6,4.3
	n	5	3	8
	Nmiss	1	3	4

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_HOMA_IR_V6_base	Mean	4.90	5.27	5.09
	Median	3.57	4.31	4.30
	SD	3.19	2.25	2.66
	MIN,MAX	2.1,11.0	3.0,9.4	2.1,11.0
	Q1,Q3	2.2,7.3	3.7,7.3	3.5,7.3
	n	7	7	14
	Nmiss	3	6	9
10%> AND 90%<=_HOMA_IR_V6_base	Mean	5.74	6.50	6.10
	Median	5.34	5.06	5.20
	SD	2.54	5.24	4.08
	MIN,MAX	1.1,14.0	1.7,34.5	1.1,34.5
	Q1,Q3	4.1,6.7	3.8,7.3	3.9,7.0
	n	103	96	199
	Nmiss	57	60	117

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_HOMA_IR_V6_base	Mean	7.52	5.69	6.63
	Median	5.99	6.05	6.05
	SD	3.89	2.54	3.39
	MIN,MAX	3.2,16.7	1.7,10.0	1.7,16.7
	Q1,Q3	4.8,10.7	3.9,7.3	4.1,8.2
	n	21	20	41
	Nmiss	15	9	24
95%>_HOMA_IR_V6_base	Mean	7.01	4.96	5.84
	Median	5.99	5.20	5.99
	SD	3.29	2.43	2.94
	MIN,MAX	3.6,12.7	1.7,10.0	1.7,12.7
	Q1,Q3	4.8,7.8	2.9,6.4	4.0,6.7
	n	9	12	21
	Nmiss	11	4	15

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_HOMA_IR_V6_base	Mean	6.73	5.16	5.69
	Median	5.51	5.20	5.51
	SD	3.52	2.65	2.90
	MIN,MAX	4.0,11.9	1.7,10.0	1.7,11.9
	Q1,Q3	4.5,8.9	3.2,6.4	4.1,6.4
	n	4	8	12
	Nmiss	9	3	12

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Laboratory results (Secondary Outcome)

5.4.1 NEFA by study visit

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
NEFA - visit 2* (mmol/L)	Mean	0.519	0.481	0.500
	Median	0.500	0.460	0.480
	SD	0.200	0.177	0.190
	MIN,MAX	0.05,1.35	0.05,1.26	0.05,1.35
	Q1,Q3	0.38,0.65	0.36,0.59	0.37,0.61
	n	189	188	377
	Nmiss	34	38	72
NEFA - visit 5* (mmol/L)	Mean	0.420	0.427	0.423
	Median	0.420	0.410	0.410
	SD	0.139	0.161	0.150
	MIN,MAX	0.08,0.78	0.11,0.89	0.08,0.89
	Q1,Q3	0.31,0.52	0.30,0.53	0.31,0.52
	n	154	144	298
	Nmiss	69	82	151

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.1 NEFA by study visit (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
NEFA - visit 6* (mmol/L)	Mean	0.465	0.455	0.460
	Median	0.450	0.430	0.440
	SD	0.181	0.194	0.187
	MIN,MAX	0.13,0.97	0.10,1.00	0.10,1.00
	Q1,Q3	0.33,0.60	0.31,0.56	0.32,0.57
	n	131	127	258
	Nmiss	92	99	191

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

Section 5. Laboratory results (Secondary Outcome)

5.4.2 IL_6 by study visit

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
IL_6 - visit 2* (pg/ml)	Mean	2.770	2.632	2.701
	Median	2.038	1.970	2.010
	SD	5.503	4.371	4.965
	MIN,MAX	0.73,75.20	0.62,58.25	0.62,75.20
	Q1,Q3	1.50,2.91	1.51,2.58	1.50,2.81
	n	189	188	377
	Nmiss	34	38	72
IL_6 - visit 5* (pg/ml)	Mean	2.733	2.379	2.562
	Median	2.243	2.142	2.199
	SD	2.158	1.186	1.763
	MIN,MAX	0.80,23.79	0.77,8.76	0.77,23.79
	Q1,Q3	1.68,3.36	1.62,2.76	1.64,2.96
	n	154	144	298
	Nmiss	69	82	151

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.2 IL_6 by study visit (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
IL_6 - visit 6* (pg/ml)	Mean	3.856	2.926	3.399
	Median	2.904	2.499	2.709
	SD	4.101	1.374	3.106
	MIN,MAX	1.07,30.77	1.10,9.37	1.07,30.77
	Q1,Q3	2.28,4.05	1.99,3.75	2.09,3.83
	n	131	127	258
	Nmiss	92	99	191

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.3 Leptin by study visit

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Leptin - visit 2* (ng/ml)	Mean	93.610	98.499	96.048
	Median	87.734	89.443	88.352
	SD	42.077	40.296	41.217
	MIN,MAX	24.19,305.25	21.93,338.66	21.93,338.66
	Q1,Q3	65.00,111.76	73.26,115.63	69.36,113.41
	n	189	188	377
	Nmiss	34	38	72
Leptin - visit 5* (ng/ml)	Mean	104.417	102.250	103.369
	Median	96.360	94.544	94.892
	SD	46.427	50.533	48.384
	MIN,MAX	25.94,376.10	18.04,453.51	18.04,453.51
	Q1,Q3	76.14,125.11	71.87,125.33	71.99,125.11
	n	154	144	298
	Nmiss	69	82	151

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Laboratory results (Secondary Outcome)

5.4.3 Leptin by study visit (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Leptin - visit 6* (ng/ml)	Mean	104.983	106.554	105.756
	Median	95.456	96.614	96.114
	SD	52.428	58.820	55.563
	MIN,MAX	21.49,397.20	31.85,505.21	21.49,505.21
	Q1,Q3	70.44,131.08	67.52,131.35	69.01,131.08
	n	131	127	258
	Nmiss	92	99	191

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

Section 5. Laboratory results (Secondary Outcome)

5.4.4 Cortisol by study visit

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Cortisol - visit 2* (nmol/l)	Mean	396.404	430.955	413.634
	Median	370.115	382.095	375.366
	SD	143.545	178.760	162.771
	MIN,MAX	154.11,869.93	145.01,1197.1	145.01,1197.1
	Q1,Q3	288.03,494.32	303.09,530.81	294.85,514.59
	n	189	188	377
	Nmiss	34	38	72
Cortisol - visit 5* (nmol/l)	Mean	716.481	777.227	745.835
	Median	673.822	738.567	720.696
	SD	230.814	252.761	243.167
	MIN,MAX	339.23,1922.5	234.30,1826.3	234.30,1922.5
	Q1,Q3	556.75,809.18	607.19,903.30	575.05,863.57
	n	154	144	298
	Nmiss	69	82	151

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Laboratory results (Secondary Outcome)

5.4.4 Cortisol by study visit (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Cortisol - visit 6* (nmol/l)	Mean	821.701	867.039	844.018
	Median	781.602	831.024	800.864
	SD	232.879	225.416	229.914
	MIN,MAX	432.38,1903.3	432.71,1859.6	432.38,1903.3
	Q1,Q3	664.85,904.55	692.19,1003.0	680.38,967.38
	n	131	127	258
	Nmiss	92	99	191

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

Section 5. Laboratory results (Secondary Outcome)

5.4.5 PAI1/PAI2 ratio by study visit

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
PAI_ratio - visit 2*	Mean	1.476	1.771	1.622
	Median	1.053	0.977	0.997
	SD	1.393	5.222	3.798
	MIN,MAX	0.28,11.89	0.33,57.63	0.28,57.63
	Q1,Q3	0.76,1.70	0.71,1.43	0.73,1.54
	n	131	128	259
	Nmiss	92	98	190
PAI_ratio - visit 6*	Mean	3.203	2.965	3.085
	Median	2.246	1.828	2.040
	SD	2.611	2.791	2.699
	MIN,MAX	0.61,13.98	0.56,16.41	0.56,16.41
	Q1,Q3	1.27,4.43	1.18,3.77	1.24,4.04
	n	131	128	259
	Nmiss	92	98	190

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 6 (36 Weeks)

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DOI: 10.3310/eme03070

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Section 5. Laboratory results (Secondary Outcome)

5.4.6 NEFA, IL-6, Leptin, Cortisol, PAI1/PAI2 ratio Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
IL_6_log_Visit6 - itt	1.116	0.0819	131	0.950	0.0781	127	-0.166	-0.283	-0.049	7.778	0.0057
Leptin_log_Visit6 - itt	4.565	0.0757	131	4.570	0.0721	127	0.005	-0.103	0.113	0.008	0.9268
Cortisol_nmol_l_log_Visit6 - itt	6.673	0.0424	131	6.734	0.0404	127	0.060	-0.001	0.121	3.815	0.0519
NEFA_log_Visit6 - itt	-0.732	0.0684	131	-0.787	0.0652	127	-0.055	-0.152	0.043	1.206	0.2731
PAI_ratio_log_Visit6 - itt	1.000	0.1243	131	0.910	0.1153	128	-0.091	-0.259	0.078	1.119	0.2911

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in tables 5.4.1 to 5.4.5 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_4_other_labs_analysis_v6.lst'
All parameters shown normal or near-normal behavior

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Section 5. Laboratory results (Secondary Outcome)

5.5.1 B12# - Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
B12 (ng/l) - visit 2	Mean	260.2	266.3	263.2
	Median	249.0	251.0	249.0
	SD	101.3	92.4	96.8
	MIN,MAX	55,760	80,745	55,760
	Q1,Q3	195,325	214,315	205,317
	n	132	131	263
	Nmiss	91	95	186
B12 below 95th - visit 2 (n(%))*	Missing	91	95	186
	Yes	121 (91.7)	121 (92.4)	242 (92.0)
	No	11 (8.3)	10 (7.6)	21 (8.0)
B12 below 5th - visit 2 (n(%))*	Missing	91	95	186
	Yes	8 (6.1)	5 (3.8)	13 (4.9)
	No	124 (93.9)	126 (96.2)	250 (95.1)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*5th centile was set at 117 ng/l and 95th centile was set at 389 ng/l
#Reference range 200-940 ng/l

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Section 5. Laboratory results (Secondary Outcome)

5.5.1 B12# - Visit 6 (36 Weeks)(Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
B12 (ng/l) - visit 6	Mean	223.7	215.0	219.3
	Median	221.0	207.5	214.0
	SD	69.6	73.2	71.5
	MIN,MAX	60,482	38,564	38,564
	Q1,Q3	178,269	174,251	175,255
	n	130	132	262
	Nmiss	93	94	187
B12 below 95th - visit 6 (n(%))*	Missing	93	94	187
	Yes	127 (97.7)	129 (97.7)	256 (97.7)
	No	3 (2.3)	3 (2.3)	6 (2.3)
B12 below 5th - visit 6 (n(%))*	Missing	93	94	187
	Yes	6 (4.6)	7 (5.3)	13 (5.0)
	No	124 (95.4)	125 (94.7)	249 (95.0)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*5th centile was set at 117 ng/l and 95th centile was set at 389 ng/l

#Reference range 200-940 ng/l

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Section 5. Laboratory results (Secondary Outcome)

5.5.2 Serum folate# - Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Serum Folate (ug/l) - visit 2	Mean	13.84	13.77	13.81
	Median	16.45	16.40	16.40
	SD	4.57	4.83	4.69
	MIN,MAX	2.6,17.5	1.7,21.0	1.7,21.0
	Q1,Q3	10.7,17.5	10.4,17.5	10.5,17.5
	n	132	131	263
	Nmiss	91	95	186
Serum Folate below 95th - visit 2 (n(%))*	Missing	91	95	186
	Yes	71 (53.8)	75 (57.3)	146 (55.5)
	No	61 (46.2)	56 (42.7)	117 (44.5)
Serum Folate below 5th - visit 2 (n(%))*	Missing	91	95	186
	Yes	0	2 (1.5)	2 (0.8)
	No	132 (100)	129 (98.5)	261 (99.2)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*5th centile was set at 2.6 ug/l and 95th centile was set at 17.5 ug/l
#Reference range 3.1-17.5 ug/l, if Serum folate value was reported as greater than 17.5 ug/l, then the value was imputed at 17.5 ug/l for summarisation

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Section 5. Laboratory results (Secondary Outcome)

5.5.2 Serum folate# - Visit 6 (36 Weeks) (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Serum Folate (ug/l) - visit 6	Mean	8.29	8.54	8.42
	Median	5.60	6.60	5.95
	SD	5.61	5.64	5.61
	MIN,MAX	1.3,17.5	1.2,21.0	1.2,21.0
	Q1,Q3	3.8,14.2	3.9,14.0	3.9,14.2
	n	132	132	264
	Nmiss	91	94	185
Serum Folate below 95th - visit 6 (n(%))*	Missing	91	94	185
	Yes	110 (83.3)	110 (83.3)	220 (83.3)
	No	22 (16.7)	22 (16.7)	44 (16.7)
Serum Folate below 5th - visit 6 (n(%))*	Missing	91	94	185
	Yes	10 (7.6)	11 (8.3)	21 (8.0)
	No	122 (92.4)	121 (91.7)	243 (92.0)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*5th centile was set at 2.6 ug/l and 95th centile was set at 17.5 ug/l

#Reference range 3.1-17.5 ug/l, if Serum folate value was reported as greater than 17.5 ug/l, then the value was imputed at 17.5 ug/l for summarisation

Section 5. Laboratory results (Secondary Outcome)

5.5.3 B12 and Serum Folate Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
B12_log_99_Visit6 - itt	5.397	0.0588	130	5.348	0.0545	132	-0.049	-0.129	0.031	1.451	0.2296
SFOLATE_log_99_Visit6 - itt	1.898	0.1264	132	1.947	0.1174	132	0.049	-0.122	0.221	0.317	0.5737

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in tables 5.5.2 and 5.6.2 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_5_B12_folate_continuo_analysis_v6.lst'
All parameters shown normal or near-normal behavior

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DOI: 10.3310/eme03070

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Section 5. Laboratory results (Secondary Outcome)

5.5.4.1 B12* - Patients below 5th centile - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of B12_N5TH by AllocatedTreatment*

B12_N5TH(Patients with B12 below 5th centile (Y/N))	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
Missing	94	93	.
Yes	7	6	13
No	125	124	249
Total	132	130	262

Frequency Missing = 187

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
b12_n5th_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.157	0.378	3.541	0.7979	1.0000

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*Analised using logistic regression (binary logit), probability modeled is B12_N5THb='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_5_5_B12_folate_discre_analysis_v6.lst'

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Section 5. Laboratory results (Secondary Outcome)

5.5.4.2 Serum Folate* - Patients below 5th centile - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of SFOL_N5TH by AllocatedTreatment*

SFOL_N5TH(Patients with Serum Folate below 5th centile (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Missing	94	91	.
Yes	11	10	21
No	121	122	243
Total	132	132	264

Frequency Missing = 185

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
sfol_n5th_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.109	0.454	2.708	0.8201	1.0000

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By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is SFOL_N5THb='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_5_5_B12_folate_discre_analysis_v6.lst'

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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.1.1 Maternal Height at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Height (cm) at Visit 2	Mean	165.1	165.5	165.3
	Median	165.0	165.0	165.0
	SD	5.9	5.9	5.9
	MIN,MAX	149,184	152,182	149,184
	Q1,Q3	161,170	162,170	161,170
	n	223	226	449
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.1.2 Maternal Height at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Height (cm) at Visit 6	Mean	166.0	166.3	166.1
	Median	166.0	166.0	166.0
	SD	6.0	5.6	5.8
	MIN,MAX	149,184	155,183	149,184
	Q1,Q3	162,170	163,171	162,170
	n	153	142	295
	Nmiss	70	84	154
Height (cm) change V6 baseline	Mean	0.1	0.2	0.2
	Median	0.0	0.0	0.0
	SD	0.8	0.8	0.8
	MIN,MAX	-2,3	-3,3	-3,3
	Q1,Q3	0,0	0,0	0,0
	n	153	142	295
	Nmiss	70	84	154

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.1.3 Maternal Height at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Height (cm) at Visit 9	Mean	165.3	166.1	165.7
	Median	165.5	166.0	166.0
	SD	5.9	5.8	5.8
	MIN,MAX	149,184	154,180	149,184
	Q1,Q3	163,169	162,171	162,170
	n	125	127	252
	Nmiss	98	99	197
Height (cm) change V9 baseline	Mean	-0.2	-0.2	-0.2
	Median	0.0	0.0	0.0
	SD	0.8	0.8	0.8
	MIN,MAX	-3,2	-3,3	-3,3
	Q1,Q3	0,0	0,0	0,0
	n	125	127	252
	Nmiss	98	99	197

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.2.1 Maternal Weight at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Weight (kg) at Visit 2	Mean	102.94	103.60	103.27
	Median	99.20	101.35	100.20
	SD	17.00	15.50	16.25
	MIN,MAX	72.0,170.4	74.0,154.8	72.0,170.4
	Q1,Q3	90.1,111.9	93.0,113.5	92.0,112.1
	n	223	226	449
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.2.2.1 Maternal Weight at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Weight (kg) at Visit 6	Mean	111.67	112.52	112.08
	Median	107.30	111.00	109.90
	SD	17.33	16.02	16.69
	MIN,MAX	79.8,166.4	79.1,165.7	79.1,166.4
	Q1,Q3	99.7,121.4	102.4,121.5	100.6,121.5
	n	156	143	299
	Nmiss	67	83	150
Weight (kg) change V6 baseline	Mean	7.23	6.70	6.97
	Median	6.93	6.50	6.80
	SD	4.91	6.00	5.45
	MIN,MAX	-5.1,19.0	-5.7,35.7	-5.7,35.7
	Q1,Q3	4.2,9.6	2.6,10.0	3.3,10.0
	n	156	143	299
	Nmiss	67	83	150

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.2.2.2 Maternal Weight at Visit 6 (36 Weeks) change from baseline - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Weight-DIFF-Visit_6 - itt	7.342	0.7601	156	6.661	0.7209	143	-0.680	-1.863	0.503	1.282	0.2585

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 6.2.2.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the means for the Weight Difference by allocated treatment,
SE represents standard error of the estimated means and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_6_2_2_Mother Anthropometry_weight_gain_v6.lst'
Parameter shown normal or near-normal behavior

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Section 6. Mother Anthropometry

6.2.3 Maternal Weight at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Weight (kg) at Visit 9	Mean	102.14	105.91	104.02
	Median	98.70	105.00	102.32
	SD	15.29	18.41	16.99
	MIN,MAX	72.7,145.8	72.9,193.0	72.7,193.0
	Q1,Q3	92.0,111.0	94.6,115.2	92.4,112.3
	n	124	124	248
	Nmiss	99	102	201
Weight (kg) change V9 baseline	Mean	-0.13	0.07	-0.03
	Median	-0.35	-0.50	-0.50
	SD	6.22	9.82	8.20
	MIN,MAX	-15.5,18.2	-19.2,79.5	-19.2,79.5
	Q1,Q3	-3.6,3.2	-4.9,2.5	-4.0,2.8
	n	124	124	248
	Nmiss	99	102	201

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.3.1 Maternal Waist at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Waist (cm) at Visit 2	Mean	108.7	110.1	109.4
	Median	106.0	109.0	108.0
	SD	13.5	11.9	12.7
	MIN,MAX	64,152	84,145	64,152
	Q1,Q3	99,117	102,117	100,117
	n	222	225	447
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.3.2 Maternal Waist at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Waist (cm) at Visit 6	Mean	120.0	119.0	119.5
	Median	120.0	119.0	119.0
	SD	13.2	11.1	12.2
	MIN,MAX	95,168	88,148	88,168
	Q1,Q3	109,128	111,126	110,127
	n	155	142	297
	Nmiss	68	84	152
Waist (cm) change V6 baseline	Mean	10.4	8.3	9.4
	Median	10.0	8.3	9.0
	SD	10.4	8.9	9.8
	MIN,MAX	-20,78	-22,29	-22,78
	Q1,Q3	5,16	4,14	4,14
	n	155	142	297
	Nmiss	68	84	152

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.3.3 Maternal Waist at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Waist (cm) at Visit 9	Mean	109.2	109.9	109.5
	Median	107.0	109.0	107.5
	SD	12.8	13.9	13.3
	MIN,MAX	80,142	79,147	79,147
	Q1,Q3	100,117	101,117	100,117
	n	124	125	249
	Nmiss	99	101	200
Waist (cm) change V9 baseline	Mean	1.5	-0.2	0.6
	Median	0.5	0.0	0.0
	SD	9.5	9.6	9.6
	MIN,MAX	-21,55	-29,34	-29,55
	Q1,Q3	-4,6	-6,4	-5,5
	n	124	125	249
	Nmiss	99	101	200

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
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Section 6. Mother Anthropometry

6.4.1 Maternal Hip at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Hip (cm) at Visit 2	Mean	126.4	127.4	126.9
	Median	125.0	126.0	125.0
	SD	12.1	11.8	11.9
	MIN,MAX	95,159	100,161	95,161
	Q1,Q3	117,134	119,135	118,134
	n	222	225	447
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.4.2 Maternal Hip at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Hip (cm) at Visit 6	Mean	130.1	131.3	130.7
	Median	128.0	130.0	129.5
	SD	12.3	11.8	12.1
	MIN,MAX	108,169	107,174	107,174
	Q1,Q3	122,139	123,140	122,139
	n	155	142	297
	Nmiss	68	84	152
Hip (cm) change V6 baseline	Mean	2.9	2.7	2.8
	Median	3.0	2.0	2.5
	SD	6.0	6.8	6.4
	MIN,MAX	-14,18	-12,21	-14,21
	Q1,Q3	-1,6	-2,7	-1,7
	n	155	142	297
	Nmiss	68	84	152

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
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Section 6. Mother Anthropometry

6.4.3 Maternal Hip at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Hip (cm) at Visit 9	Mean	127.3	128.6	128.0
	Median	126.0	128.0	127.0
	SD	12.2	13.4	12.8
	MIN,MAX	99,166	79,167	79,167
	Q1,Q3	120,135	121,137	120,136
	n	124	125	249
	Nmiss	99	101	200
Hip (cm) change V9 baseline	Mean	1.1	-0.0	0.5
	Median	1.3	0.0	1.0
	SD	6.8	7.8	7.3
	MIN,MAX	-19,17	-41,23	-41,23
	Q1,Q3	-3,6	-4,5	-4,5
	n	124	125	249
	Nmiss	99	101	200

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.5.1 Maternal Mid Arm at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Mid Arm (cm) at Visit 2	Mean	36.3	36.7	36.5
	Median	36.0	36.0	36.0
	SD	5.0	4.7	4.8
	MIN,MAX	20,54	28,52	20,54
	Q1,Q3	33,39	34,39	34,39
	n	220	221	441
	Nmiss	3	5	8

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Section 6. Mother Anthropometry

6.5.2 Maternal Mid Arm at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Mid Arm (cm) at Visit 6	Mean	36.5	36.5	36.5
	Median	36.0	36.0	36.0
	SD	4.9	4.4	4.7
	MIN,MAX	22,56	22,52	22,56
	Q1,Q3	33,39	34,39	34,39
	n	154	142	296
	Nmiss	69	84	153
Mid Arm (cm) change V6 baseline	Mean	-0.1	-0.8	-0.4
	Median	0.0	-0.5	-0.4
	SD	3.8	4.0	3.9
	MIN,MAX	-10,12	-20,9	-20,12
	Q1,Q3	-2,2	-2,1	-2,1
	n	153	140	293
	Nmiss	70	86	156

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.5.3 Maternal Mid Arm at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Mid Arm (cm) at Visit 9	Mean	37.1	37.4	37.2
	Median	36.5	37.0	37.0
	SD	4.7	4.4	4.5
	MIN,MAX	28,53	28,54	28,54
	Q1,Q3	34,39	34,40	34,40
	n	123	125	248
	Nmiss	100	101	201
Mid Arm (cm) change V9 baseline	Mean	0.7	0.0	0.3
	Median	0.3	0.0	0.0
	SD	4.4	3.8	4.1
	MIN,MAX	-7,25	-9,13	-9,25
	Q1,Q3	-2,3	-2,2	-2,3
	n	122	123	245
	Nmiss	101	103	204

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Section 6. Mother Anthropometry

6.6.1 Maternal Mid Thigh at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Mid Thigh (cm) at Visit 2	Mean	64.2	64.2	64.2
	Median	64.0	63.0	64.0
	SD	7.7	6.9	7.3
	MIN,MAX	25,84	50,89	25,89
	Q1,Q3	60,69	60,68	60,69
	n	219	222	441
	Nmiss	4	4	8

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.6.2 Maternal Mid Thigh at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Mid Thigh (cm) at Visit 6	Mean	65.3	65.2	65.3
	Median	65.0	65.0	65.0
	SD	7.4	6.8	7.1
	MIN,MAX	29,85	45,83	29,85
	Q1,Q3	60,70	60,69	60,70
	n	154	139	293
	Nmiss	69	87	156
Mid Thigh (cm) change V6 baseline	Mean	0.8	0.1	0.5
	Median	0.0	1.0	0.6
	SD	5.7	6.1	5.9
	MIN,MAX	-12,28	-30,14	-30,28
	Q1,Q3	-3,4	-4,4	-3,4
	n	152	137	289
	Nmiss	71	89	160

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6.6.3 Maternal Mid Thigh at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Mid Thigh (cm) at Visit 9	Mean	64.3	65.8	65.1
	Median	64.3	65.0	64.8
	SD	6.7	6.8	6.8
	MIN,MAX	51,84	52,84	51,84
	Q1,Q3	59,68	61,70	60,70
	n	122	124	246
	Nmiss	101	102	203
Mid Thigh (cm) change V9 baseline	Mean	0.7	0.7	0.7
	Median	0.0	1.0	0.5
	SD	6.8	5.7	6.3
	MIN,MAX	-10,47	-19,21	-19,47
	Q1,Q3	-4,4	-3,4	-4,4
	n	120	122	242
	Nmiss	103	104	207

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Section 6. Mother Anthropometry

6.7.1 Maternal Tricep Skinfold at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Tricep Skinfold (mm) at Visit 2	Mean	31.2	31.9	31.6
	Median	30.6	31.0	30.8
	SD	9.7	10.8	10.2
	MIN,MAX	5,62	8,66	5,66
	Q1,Q3	25,38	24,39	25,38
	n	222	222	444
	Nmiss	1	4	5

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6.7.2 Maternal Tricep Skinfold at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Tricep Skinfold (mm) at Visit 6	Mean	30.4	31.3	30.9
	Median	30.5	30.0	30.0
	SD	10.3	12.0	11.1
	MIN,MAX	9,65	9,80	9,80
	Q1,Q3	23,36	24,36	23,36
	n	155	143	298
	Nmiss	68	83	151
Tricep Skinfold (mm) change V6 baseline	Mean	-1.0	-0.3	-0.7
	Median	-1.2	0.4	-0.3
	SD	10.3	12.2	11.2
	MIN,MAX	-31,32	-44,34	-44,34
	Q1,Q3	-7,5	-6,6	-6,5
	n	154	141	295
	Nmiss	69	85	154

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.7.3 Maternal Tricep Skinfold at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Tricep Skinfold (mm) at Visit 9	Mean	32.2	33.4	32.8
	Median	32.0	32.0	32.0
	SD	10.8	11.4	11.1
	MIN,MAX	8,77	13,110	8,110
	Q1,Q3	25,38	27,39	26,39
	n	123	125	248
	Nmiss	100	101	201
Tricep Skinfold (mm) change V9 baseline	Mean	1.0	1.3	1.2
	Median	0.0	0.0	0.0
	SD	10.5	11.5	11.0
	MIN,MAX	-32,37	-26,64	-32,64
	Q1,Q3	-6,6	-6,7	-6,6
	n	122	124	246
	Nmiss	101	102	203

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Section 6. Mother Anthropometry

6.8.1 Maternal Bicep Skinfold at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Bicep Skinfold (mm) at Visit 2	Mean	25.7	27.4	26.6
	Median	24.2	25.8	25.0
	SD	10.0	10.9	10.5
	MIN,MAX	1,60	9,61	1,61
	Q1,Q3	20,31	20,34	20,32
	n	222	222	444
	Nmiss	1	4	5

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

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Section 6. Mother Anthropometry

6.8.2 Maternal Bicep Skinfold at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Bicep Skinfold (mm) at Visit 6	Mean	26.0	26.9	26.5
	Median	25.0	25.0	25.0
	SD	10.5	11.6	11.0
	MIN,MAX	8,66	7,71	7,71
	Q1,Q3	19,33	19,31	19,33
	n	155	143	298
	Nmiss	68	83	151
Bicep Skinfold (mm) change V6 baseline	Mean	-0.2	-0.5	-0.3
	Median	-0.1	-1.0	-0.6
	SD	11.1	10.7	10.9
	MIN,MAX	-42,35	-26,35	-42,35
	Q1,Q3	-7,7	-6,4	-7,5
	n	154	141	295
	Nmiss	69	85	154

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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6.8.3 Maternal Bicep Skinfold at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Bicep Skinfold (mm) at Visit 9	Mean	27.2	29.7	28.5
	Median	25.0	27.0	25.8
	SD	12.1	15.1	13.7
	MIN,MAX	9,70	8,120	8,120
	Q1,Q3	20,31	21,35	20,34
	n	123	125	248
	Nmiss	100	101	201
Bicep Skinfold (mm) change V9 baseline	Mean	0.6	2.4	1.5
	Median	-0.9	2.0	0.5
	SD	11.8	12.6	12.2
	MIN,MAX	-35,39	-20,76	-35,76
	Q1,Q3	-7,8	-4,7	-6,7
	n	122	124	246
	Nmiss	101	102	203

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.9.1 Maternal Subscapular Skinfold at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Subscapular Skinfold (mm) at Visit 2	Mean	32.0	32.6	32.3
	Median	32.7	31.3	32.0
	SD	12.2	11.8	12.0
	MIN,MAX	3,68	8,71	3,71
	Q1,Q3	24,40	25,39	24,39
	n	222	220	442
	Nmiss	1	6	7

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.9.2 Maternal Subscapular Skinfold at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Subscapular Skinfold (mm) at Visit 6	Mean	32.7	34.5	33.5
	Median	31.4	34.0	32.0
	SD	13.5	13.9	13.7
	MIN,MAX	3,71	5,77	3,77
	Q1,Q3	24,40	25,41	25,41
	n	154	141	295
	Nmiss	69	85	154
Subscapular Skinfold (mm) change V6 base	Mean	-0.2	1.3	0.5
	Median	-1.5	1.0	0.0
	SD	12.0	10.7	11.4
	MIN,MAX	-32,39	-23,38	-32,39
	Q1,Q3	-7,6	-5,7	-6,7
	n	153	137	290
	Nmiss	70	89	159

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.9.3 Maternal Subscapular Skinfold at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Subscapular Skinfold (mm) at Visit 9	Mean	33.2	35.9	34.6
	Median	31.0	34.0	33.0
	SD	13.1	13.2	13.2
	MIN,MAX	6,83	9,81	6,83
	Q1,Q3	24,40	28,44	26,42
	n	123	124	247
	Nmiss	100	102	202
Subscapular Skinfold (mm) change V9 base	Mean	1.2	1.7	1.4
	Median	-0.2	2.6	1.0
	SD	11.6	12.6	12.1
	MIN,MAX	-28,47	-31,56	-31,56
	Q1,Q3	-6,7	-7,9	-6,9
	n	122	122	244
	Nmiss	101	104	205

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.10.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated BMI (kg/m^2) at Visit 2	Mean	37.7	37.8	37.7
	Median	36.7	36.9	36.8
	SD	5.6	4.9	5.3
	MIN,MAX	30,61	30,57	30,61
	Q1,Q3	33,41	34,41	34,41
	n	223	226	449
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.10.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated BMI (kg/m^2) at Visit 6	Mean	40.4	40.6	40.5
	Median	39.6	39.8	39.7
	SD	5.4	4.9	5.2
	MIN,MAX	31,56	32,55	31,56
	Q1,Q3	36,44	37,44	37,44
	n	153	141	294
	Nmiss	70	85	155
Calculated BMI (kg/m^2) change V6 baseli	Mean	2.5	2.4	2.5
	Median	2.4	2.5	2.4
	SD	1.8	2.1	2.0
	MIN,MAX	-3,7	-2,12	-3,12
	Q1,Q3	2,4	1,3	1,4
	n	153	141	294
	Nmiss	70	85	155

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
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Section 6. Mother Anthropometry

6.10.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and ist change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Calculated BMI (kg/m^2) at Visit 9	Mean	37.4	38.3	37.8
	Median	37.3	37.9	37.5
	SD	5.2	5.6	5.4
	MIN,MAX	28,61	29,61	28,61
	Q1,Q3	34,40	34,42	34,41
	n	124	124	248
	Nmiss	99	102	201
Calculated BMI (kg/m^2) change V9 baseli	Mean	0.0	0.1	0.0
	Median	-0.0	-0.2	-0.1
	SD	2.2	3.3	2.8
	MIN,MAX	-5,5	-7,25	-7,25
	Q1,Q3	-1,1	-2,1	-1,1
	n	124	124	248
	Nmiss	99	102	201

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.11 Maternal body percentage fat (Edinburgh)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 1	Mean	46.82	48.19	47.54
	Median	46.85	48.00	47.50
	SD	5.62	5.18	5.41
	MIN,MAX	33.9,59.0	34.3,58.7	33.9,59.0
	Q1,Q3	42.6,50.4	45.3,51.7	44.8,51.1
	n	48	53	101
	Nmiss	12	7	19
Fat (%) Visit 6	Mean	46.30	47.48	46.88
	Median	47.10	47.65	47.30
	SD	4.84	4.63	4.74
	MIN,MAX	34.3,53.9	39.1,56.3	34.3,56.3
	Q1,Q3	43.9,48.8	43.9,51.2	43.9,50.2
	n	31	30	61
	Nmiss	29	30	59

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*This summary is only applicable to Edinburgh patients
#Data have been checked, innacuracies happened at time and point
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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.11 Maternal body percentage fat (Edinburgh) (Cont.)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 9	Mean	47.45	48.35	47.91
	Median	48.10	47.30	48.00
	SD	4.97	5.31	5.12
	MIN,MAX	36.6,54.6	37.9,58.6	36.6,58.6
	Q1,Q3	43.6,51.9	44.6,53.1	44.4,52.0
	n	29	30	59
	Nmiss	31	30	61

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.12 Maternal Body fat mass (Edinburgh)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 1	Mean	47.927	50.325	49.185
	Median	45.854	49.384	47.509
	SD	12.054	11.787	11.916
	MIN,MAX	29.91,96.83	26.82,76.17	26.82,96.83
	Q1,Q3	38.65,54.37	42.17,59.48	41.17,55.54
	n	48	53	101
	Nmiss	12	7	19
FatMass (kg) Visit 6	Mean	50.827	54.372	52.570
	Median	50.278	54.583	50.690
	SD	10.944	12.172	11.606
	MIN,MAX	27.38,89.22	30.52,76.38	27.38,89.22
	Q1,Q3	46.87,55.44	46.75,65.08	46.86,57.92
	n	31	30	61
	Nmiss	29	30	59

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*This summary is only applicable to Edinburgh patients
#Data have been checked, innacuracies happened at time and point
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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.12 Maternal Body fat mass (Edinburgh) (Cont.)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 9	Mean	49.063	50.086	49.583
	Median	51.265	48.549	50.263
	SD	9.011	13.726	11.562
	MIN,MAX	26.64,63.25	13.56,75.76	13.56,75.76
	Q1,Q3	46.31,55.43	45.10,59.07	45.10,56.26
	n	29	30	59
	Nmiss	31	30	61

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.13 Maternal Body mass (Edinburgh)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BodyMass (kg) Visit 1	Mean	101.388	103.322	102.413
	Median	97.810	104.018	100.077
	SD	16.190	15.961	16.017
	MIN,MAX	74.97,170.25	73.54,140.37	73.54,170.25
	Q1,Q3	89.72,111.83	92.19,112.90	90.53,112.40
	n	47	53	100
	Nmiss	13	7	20
BodyMass (kg) Visit 6	Mean	108.794	113.366	111.043
	Median	105.046	111.525	108.272
	SD	14.871	16.740	15.853
	MIN,MAX	79.82,165.47	78.11,147.87	78.11,165.47
	Q1,Q3	100.32,117.60	104.43,124.68	102.65,118.64
	n	31	30	61
	Nmiss	29	30	59

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*This summary is only applicable to Edinburgh patients
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.13 Maternal Body mass (Edinburgh) (Cont.)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BodyMass (kg) Visit 9	Mean	102.821	106.471	104.677
	Median	102.540	105.399	104.190
	SD	12.759	16.507	14.772
	MIN,MAX	72.74,126.73	73.76,146.86	72.74,146.86
	Q1,Q3	96.36,112.37	98.50,115.30	96.80,114.25
	n	29	30	59
	Nmiss	31	30	61

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.2.2.2.extra Maternal Weight at Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Weight-Visit_6 - itt	112.473	0.7582	156	111.836	0.7209	143	-0.637	-1.819	0.544	1.127	0.2893

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Summary statistics are presented in table 6.2.2.1 of this report
Outcome analysed using a linear regression model, ajusted by weight_V2, BMI band and centre.
Significance level set at p<0.05. Estimated mean represents the means for the Weight by allocated treatment,
SE represents standard error of the estimated means and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_6_2_2_Mother_Anthropometry_weight_v6.lst'
Parameter shown normal or near-normal behavior

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Section 7. Baby Anthropometry - All Patients

7.1.1.1 Baby Age and Weight at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Neonatal Age (days)-V8	Mean	1.04	0.95	1.00
	Median	1.00	0.00	0.00
	SD	2.44	2.42	2.43
	MIN,MAX	0.0,26.0	0.0,23.0	0.0,26.0
	Q1,Q3	0.0,1.0	0.0,1.0	0.0,1.0
	n	157	147	304
	Nmiss	66	79	145
Baby Weight* (g)-V8	Mean	3687.72	3447.81	3574.28
	Median	3510.00	3432.50	3460.00
	SD	2689.82	546.15	1989.47
	MIN,MAX	400.0,37141	2110.0,4900.0	400.0,37141
	Q1,Q3	3110.0,3860.0	3077.5,3810.0	3090.0,3850.0
	n	165	148	313
	Nmiss	58	78	136

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*this is the recorded weight, done for a second time and it is different from the one presented in table 4.1.1.2.2.1

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.1.2 Baby Lenght and Ponderal Index at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Length (cm)-V8	Mean	50.23	49.64	49.94
	Median	51.50	50.00	51.00
	SD	8.16	7.98	8.06
	MIN,MAX	0.0,63.5	0.0,61.0	0.0,63.5
	Q1,Q3	49.5,53.0	48.0,53.0	49.0,53.0
	n	153	143	296
	Nmiss	70	83	153
Baby ponderal index* -V8	Mean	3.01	2.67	2.85
	Median	2.54	2.61	2.57
	SD	3.68	0.50	2.69
	MIN,MAX	1.7,40.6	1.5,5.0	1.5,40.6
	Q1,Q3	2.3,2.8	2.4,2.9	2.3,2.9
	n	145	131	276
	Nmiss	78	95	173

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.1.3 Baby Head Circumference and Skinfold Triceps at Visit 8 (Delivery)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Head Circumfe (cm)-V8	Mean	34.71	34.78	34.74
	Median	35.00	35.00	35.00
	SD	4.20	3.55	3.89
	MIN,MAX	0.0,41.5	0.0,53.0	0.0,53.0
	Q1,Q3	34.0,36.0	34.0,36.0	34.0,36.0
	n	164	153	317
	Nmiss	59	73	132
Baby Skinfold Triceps (mm)-V8	Mean	14.34	16.42	15.32
	Median	7.00	6.50	6.75
	SD	20.63	27.87	24.28
	MIN,MAX	0.0,90.0	0.0,162.0	0.0,162.0
	Q1,Q3	5.0,9.5	5.0,10.0	5.0,9.5
	n	111	99	210
	Nmiss	112	127	239

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.1.4 Baby Skinfold Subscapular and fat at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Skinfold Subscapular (mm)- V8	Mean	13.46	15.69	14.49
	Median	6.00	6.15	6.00
	SD	20.44	27.96	24.19
	MIN,MAX	0.0,100.0	0.0,158.0	0.0,158.0
	Q1,Q3	5.0,9.5	5.0,9.0	5.0,9.5
	n	113	98	211
	Nmiss	110	128	238
BABY_FAT* (%)-V8	Mean	12.08	12.86	12.46
	Median	10.95	12.30	12.30
	SD	5.74	4.47	5.11
	MIN,MAX	1.0,24.3	5.7,20.6	1.0,24.3
	Q1,Q3	8.1,17.1	10.0,16.2	8.1,16.5
	n	22	21	43
	Nmiss	201	205	406

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.1.5 Baby Fat Mass and Body mass at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
BABY_FatMass* (kg)-V8	Mean	0.43259	0.44833	0.44028
	Median	0.39545	0.44260	0.43290
	SD	0.24801	0.19505	0.22121
	MIN,MAX	0.0247,0.9767	0.1421,0.7902	0.0247,0.9767
	Q1,Q3	0.2703,0.6053	0.2933,0.5896	0.2703,0.6053
	n	22	21	43
	Nmiss	201	205	406
BABY_BodyMass* (kg)-V8	Mean	3.39626	3.37760	3.38715
	Median	3.38680	3.42610	3.41780
	SD	0.50097	0.41133	0.45403
	MIN,MAX	2.4244,4.4472	2.5026,3.9902	2.4244,4.4472
	Q1,Q3	3.0944,3.6853	3.1039,3.7412	3.0944,3.7141
	n	22	21	43
	Nmiss	201	205	406

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat Mass and Body Mass was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.2.1 Baby Age and Weight at Visit 9 (Final 3 months postnatal)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Neonatal Age (days)-V9	Mean	99.59	97.72	98.65
	Median	96.00	94.00	95.00
	SD	13.12	14.01	13.58
	MIN,MAX	59.0,143.0	53.0,172.0	53.0,172.0
	Q1,Q3	92.0,105.5	91.0,103.0	91.0,104.0
	n	128	129	257
	Nmiss	95	97	192
Baby Weight (g)-V9	Mean	6085.04	5971.97	6027.64
	Median	6205.50	6075.00	6156.60
	SD	1276.59	1724.20	1518.54
	MIN,MAX	666.0,8883.0	90.2,12500	90.2,12500
	Q1,Q3	5598.0,6845.0	5556.4,6735.0	5580.0,6795.0
	n	128	132	260
	Nmiss	95	94	189

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.2.2 Baby Lenght and Ponderal Index at Visit 9 (Final 3 months postnatal)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Length (cm)-V9	Mean	66.47	61.69	64.08
	Median	62.00	62.00	62.00
	SD	48.75	6.33	34.77
	MIN,MAX	41.0,605.0	5.7,74.0	5.7,605.0
	Q1,Q3	60.0,64.5	60.0,64.0	60.0,64.3
	n	125	125	250
	Nmiss	98	101	199
Baby ponderal index* -V9	Mean	2.58	28.76	15.72
	Median	2.53	2.54	2.54
	SD	0.82	293.42	207.90
	MIN,MAX	0.0,8.9	0.0,3283.1	0.0,3283.1
	Q1,Q3	2.4,2.8	2.3,2.8	2.3,2.8
	n	124	125	249
	Nmiss	99	101	200

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Baby Anthropometry - All Patients

7.1.2.3 Baby Head Circumference and Skinfold Triceps at Visit 9 (Final 3 months postnatal)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Head Circumfe (cm)-V9	Mean	41.30	41.02	41.16
	Median	41.00	41.00	41.00
	SD	2.87	4.42	3.72
	MIN,MAX	34.8,62.0	4.0,62.0	4.0,62.0
	Q1,Q3	40.0,42.6	39.8,42.5	40.0,42.5
	n	124	122	246
	Nmiss	99	104	203
BabySkinfoldTriceps (mm)-V9	Mean	22.05	24.61	23.32
	Median	10.40	11.00	11.00
	SD	33.17	34.59	33.82
	MIN,MAX	0.7,160.2	0.8,170.2	0.7,170.2
	Q1,Q3	8.0,15.0	9.0,15.0	9.0,15.0
	n	106	104	210
	Nmiss	117	122	239

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.2.4 Baby Skinfold Subscapular and fat at Visit 9 (Final 3 months postnatal)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
BabySkinfoldSubscapular (mm)-V9	Mean	17.00	23.11	20.05
	Median	8.65	10.00	9.00
	SD	23.95	31.33	27.99
	MIN,MAX	0.5,106.0	0.7,162.0	0.5,162.0
	Q1,Q3	7.0,11.0	7.4,14.9	7.0,13.0
	n	104	104	208
	Nmiss	119	122	241
BABY_FAT* (%)-V9	Mean	25.88	23.19	24.58
	Median	24.10	23.50	23.55
	SD	6.13	5.91	6.13
	MIN,MAX	15.1,41.6	12.0,32.3	12.0,41.6
	Q1,Q3	21.5,29.7	19.6,27.8	21.2,28.8
	n	31	29	60
	Nmiss	192	197	389

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Baby Anthropometry - All Patients

7.1.2.5 Baby Fat Mass and Body mass at Visit 9 (Final 3 months postnatal)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
BABY_FatMass* (kg)-V9	Mean	3.00671	1.41993	2.23977
	Median	1.53930	1.42560	1.49110
	SD	8.04716	0.50009	5.80390
	MIN,MAX	0.8625,46.309	0.5693,2.4550	0.5693,46.309
	Q1,Q3	1.1952,1.9387	1.0391,1.7338	1.1552,1.8330
	n	31	29	60
	Nmiss	192	197	389
BABY_BodyMass* (kg)-V9	Mean	9.68262	6.01111	7.91017
	Median	6.22815	6.10320	6.16140
	SD	19.4087	0.92006	13.9814
	MIN,MAX	4.8014,112.37	4.4105,8.0110	4.4105,112.37
	Q1,Q3	5.6061,6.5379	5.2742,6.5058	5.4949,6.5379
	n	30	28	58
	Nmiss	193	198	391

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat Mass and Body Mass was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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DOI: 10.3310/eme03070

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.1 Baby Age and Weight at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Neonatal Age (days)-V8	Mean	1.04	0.97	1.00
	Median	1.00	0.00	0.00
	SD	2.44	2.44	2.44
	MIN,MAX	0.0,26.0	0.0,23.0	0.0,26.0
	Q1,Q3	0.0,1.0	0.0,1.0	0.0,1.0
	n	157	145	302
	Nmiss	63	69	132
Baby Weight* (g)-V8	Mean	3707.76	3455.18	3588.80
	Median	3515.00	3437.50	3460.00
	SD	2685.66	545.08	1990.02
	MIN,MAX	1490.0,37141	2110.0,4900.0	1490.0,37141
	Q1,Q3	3115.0,3865.0	3080.0,3820.0	3090.0,3860.0
	n	164	146	310
	Nmiss	56	68	124

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*this is the recorded weight, done for a second time and it is different from the one presented in table 4.1.1.2.2.1

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.2.1 Baby Lenght and Ponderal Index at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Length (cm)-V8	Mean	50.23	49.66	49.95
	Median	51.50	50.00	51.00
	SD	8.16	8.00	8.07
	MIN,MAX	0.0,63.5	0.0,61.0	0.0,63.5
	Q1,Q3	49.5,53.0	48.0,53.0	49.0,53.0
	n	153	142	295
	Nmiss	67	72	139
Baby ponderal index* -V8	Mean	3.01	2.67	2.85
	Median	2.54	2.61	2.57
	SD	3.68	0.50	2.69
	MIN,MAX	1.7,40.6	1.5,5.0	1.5,40.6
	Q1,Q3	2.3,2.8	2.4,2.9	2.3,2.9
	n	145	130	275
	Nmiss	75	84	159

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.2.2 Ponderal index #,$ - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
baby_ponderal_alive_log - itt	0.954	0.0241	143	0.986	0.0244	130	0.031	-0.004	0.066	3.007	0.0841

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Summary statistics are presented in table 7.2.1.2.1 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05. Estimated mean represents the mean of the log transformed variable by allocated treatment,Parameter shown normal or near-normal behavior
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_7_2_2_Baby_Ponderal_delivery.lst'
#Ponderal index was calculated using the following formula: (100*(baby_weight_in_g))/((baby_lenght_in_cm)^3),
$Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

Section 7. Baby Anthropometry - Only Alive Births

7.2.1.3 Baby Head Circumference and Skinfold Triceps at Visit 8 (Delivery)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Head Circumfe (cm)-V8	Mean	34.71	34.80	34.75
	Median	35.00	35.00	35.00
	SD	4.20	3.55	3.90
	MIN,MAX	0.0,41.5	0.0,53.0	0.0,53.0
	Q1,Q3	34.0,36.0	34.0,36.0	34.0,36.0
	n	164	152	316
	Nmiss	56	62	118
Baby Skinfold Triceps (mm)-V8	Mean	14.34	16.42	15.32
	Median	7.00	6.50	6.75
	SD	20.63	27.87	24.28
	MIN,MAX	0.0,90.0	0.0,162.0	0.0,162.0
	Q1,Q3	5.0,9.5	5.0,10.0	5.0,9.5
	n	111	99	210
	Nmiss	109	115	224

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.4 Baby Skinfold Subscapular and fat at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Skinfold Subscapular (mm)- V8	Mean	13.46	15.69	14.49
	Median	6.00	6.15	6.00
	SD	20.44	27.96	24.19
	MIN,MAX	0.0,100.0	0.0,158.0	0.0,158.0
	Q1,Q3	5.0,9.5	5.0,9.0	5.0,9.5
	n	113	98	211
	Nmiss	107	116	223
BABY_FAT* (%)-V8	Mean	12.08	12.86	12.46
	Median	10.95	12.30	12.30
	SD	5.74	4.47	5.11
	MIN,MAX	1.0,24.3	5.7,20.6	1.0,24.3
	Q1,Q3	8.1,17.1	10.0,16.2	8.1,16.5
	n	22	21	43
	Nmiss	198	193	391

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.5 Baby Fat Mass and Body mass at Visit 8 (Delivery)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
BABY_FatMass* (kg)-V8	Mean	0.43259	0.44833	0.44028
	Median	0.39545	0.44260	0.43290
	SD	0.24801	0.19505	0.22121
	MIN,MAX	0.0247,0.9767	0.1421,0.7902	0.0247,0.9767
	Q1,Q3	0.2703,0.6053	0.2933,0.5896	0.2703,0.6053
	n	22	21	43
	Nmiss	198	193	391
BABY_BodyMass* (kg)-V8	Mean	3.39626	3.37760	3.38715
	Median	3.38680	3.42610	3.41780
	SD	0.50097	0.41133	0.45403
	MIN,MAX	2.4244,4.4472	2.5026,3.9902	2.4244,4.4472
	Q1,Q3	3.0944,3.6853	3.1039,3.7412	3.0944,3.7141
	n	22	21	43
	Nmiss	198	193	391

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat Mass and Body Mass was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.1 Baby Age and Weight at Visit 9 (Final 3 months postnatal)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Neonatal Age (days)-V9	Mean	99.59	97.72	98.65
	Median	96.00	94.00	95.00
	SD	13.12	14.01	13.58
	MIN,MAX	59.0,143.0	53.0,172.0	53.0,172.0
	Q1,Q3	92.0,105.5	91.0,103.0	91.0,104.0
	n	128	129	257
	Nmiss	92	85	177
Baby Weight (g)-V9	Mean	6085.04	5971.97	6027.64
	Median	6205.50	6075.00	6156.60
	SD	1276.59	1724.20	1518.54
	MIN,MAX	666.0,8883.0	90.2,12500	90.2,12500
	Q1,Q3	5598.0,6845.0	5556.4,6735.0	5580.0,6795.0
	n	128	132	260
	Nmiss	87	77	164

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.2 Baby Lenght and Ponderal Index at Visit 9 (Final 3 months postnatal)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Length (cm)-V9	Mean	66.47	61.69	64.08
	Median	62.00	62.00	62.00
	SD	48.75	6.33	34.77
	MIN,MAX	41.0,605.0	5.7,74.0	5.7,605.0
	Q1,Q3	60.0,64.5	60.0,64.0	60.0,64.3
	n	125	125	250
	Nmiss	90	84	174
Baby ponderal index* -V9	Mean	2.58	28.76	15.72
	Median	2.53	2.54	2.54
	SD	0.82	293.42	207.90
	MIN,MAX	0.0,8.9	0.0,3283.1	0.0,3283.1
	Q1,Q3	2.4,2.8	2.3,2.8	2.3,2.8
	n	124	125	249
	Nmiss	91	84	175

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.3 Baby Head Circumference and Skinfold Triceps at Visit 9 (Final 3 months postnatal)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Head Circumfe (cm)-V9	Mean	41.30	41.02	41.16
	Median	41.00	41.00	41.00
	SD	2.87	4.42	3.72
	MIN,MAX	34.8,62.0	4.0,62.0	4.0,62.0
	Q1,Q3	40.0,42.6	39.8,42.5	40.0,42.5
	n	124	122	246
	Nmiss	91	87	178
BabySkinfoldTriceps (mm)-V9	Mean	22.05	24.61	23.32
	Median	10.40	11.00	11.00
	SD	33.17	34.59	33.82
	MIN,MAX	0.7,160.2	0.8,170.2	0.7,170.2
	Q1,Q3	8.0,15.0	9.0,15.0	9.0,15.0
	n	106	104	210
	Nmiss	109	105	214

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.4 Baby Skinfold Subscapular and fat at Visit 9 (Final 3 months postnatal)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
BabySkinfoldSubscapular (mm)-V9	Mean	17.00	23.11	20.05
	Median	8.65	10.00	9.00
	SD	23.95	31.33	27.99
	MIN,MAX	0.5,106.0	0.7,162.0	0.5,162.0
	Q1,Q3	7.0,11.0	7.4,14.9	7.0,13.0
	n	104	104	208
	Nmiss	111	105	216
BABY_FAT* (%)-V9	Mean	25.88	23.19	24.58
	Median	24.10	23.50	23.55
	SD	6.13	5.91	6.13
	MIN,MAX	15.1,41.6	12.0,32.3	12.0,41.6
	Q1,Q3	21.5,29.7	19.6,27.8	21.2,28.8
	n	31	29	60
	Nmiss	184	180	364

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.5 Baby Fat Mass and Body mass at Visit 9 (Final 3 months postnatal)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
BABY_FatMass* (kg)-V9	Mean	3.00671	1.41993	2.23977
	Median	1.53930	1.42560	1.49110
	SD	8.04716	0.50009	5.80390
	MIN,MAX	0.8625,46.309	0.5693,2.4550	0.5693,46.309
	Q1,Q3	1.1952,1.9387	1.0391,1.7338	1.1552,1.8330
	n	31	29	60
	Nmiss	184	180	364
BABY_BodyMass* (kg)-V9	Mean	9.68262	6.01111	7.91017
	Median	6.22815	6.10320	6.16140
	SD	19.4087	0.92006	13.9814
	MIN,MAX	4.8014,112.37	4.4105,8.0110	4.4105,112.37
	Q1,Q3	5.6061,6.5379	5.2742,6.5058	5.4949,6.5379
	n	30	28	58
	Nmiss	185	181	366

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat Mass and Body Mass was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.3 Baby Ponderal Index at Visit 8 (Delivery) and Visit 9 (Final 3 months postnatal)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby ponderal index* -V8	Mean	2.60	2.67	2.63
	Median	2.53	2.61	2.56
	SD	0.41	0.50	0.46
	MIN,MAX	1.7,3.9	1.5,5.0	1.5,5.0
	Q1,Q3	2.3,2.8	2.4,2.9	2.3,2.9
	n	143	130	273
	Nmiss	77	84	161
Baby ponderal index* -V9	Mean	2.58	2.52	2.55
	Median	2.53	2.54	2.53
	SD	0.82	1.00	0.92
	MIN,MAX	0.0,8.9	0.0,9.8	0.0,9.8
	Q1,Q3	2.4,2.8	2.3,2.8	2.3,2.8
	n	124	124	248
	Nmiss	91	85	176

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

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Section 7. Baby Anthropometry - Only Alive Births

7.2.4 Baby Weight at Visit 8 (Delivery) and Visit 9 (Final 3 months postnatal)#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Weight* (g)-V8	Mean	3502.65	3455.18	3480.22
	Median	3510.00	3437.50	3460.00
	SD	561.32	545.08	553.32
	MIN,MAX	1490.0,5060.0	2110.0,4900.0	1490.0,5060.0
	Q1,Q3	3110.0,3860.0	3080.0,3820.0	3090.0,3850.0
	n	163	146	309
	Nmiss	57	68	125
Baby Weight (g)-V9	Mean	6085.04	5971.97	6027.64
	Median	6205.50	6075.00	6156.60
	SD	1276.59	1724.20	1518.54
	MIN,MAX	666.0,8883.0	90.2,12500	90.2,12500
	Q1,Q3	5598.0,6845.0	5556.4,6735.0	5580.0,6795.0
	n	128	132	260
	Nmiss	87	77	164

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*this is the recorded weight, done for a second time and it is different from the one presented in table 4.1.1.2.2.1

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

Section 7. Baby Anthropometry - Only Alive Births

7.2.5 Baby Lenght at Visit 8 (Delivery) and Visit 9 (Final 3 months postnatal)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Baby Length (cm)-V8	Mean	51.24	50.73	50.99
	Median	51.90	50.50	51.00
	SD	4.01	3.26	3.67
	MIN,MAX	20.5,63.5	43.0,61.0	20.5,63.5
	Q1,Q3	49.5,53.0	48.0,53.0	49.0,53.0
	n	150	139	289
	Nmiss	70	75	145
Baby Length (cm)-V9	Mean	62.13	61.69	61.91
	Median	62.00	62.00	62.00
	SD	4.38	6.33	5.44
	MIN,MAX	41.0,73.0	5.7,74.0	5.7,74.0
	Q1,Q3	60.0,64.4	60.0,64.0	60.0,64.2
	n	124	125	249
	Nmiss	91	84	175

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.1 CRP - Visit 3 Randomisation (10-16 Weeks) and Visit 5 (28 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
CRP - V3 (mg/L)	Mean	11.11	10.70	10.90
	Median	9.00	9.00	9.00
	SD	7.39	6.85	7.12
	MIN,MAX	1.0,49.0	0.0,45.0	0.0,49.0
	Q1,Q3	6.0,15.0	5.0,14.0	5.5,15.0
	n	221	223	444
	Nmiss	2	3	5
CRP - V5 (mg/L)	Mean	10.65	9.78	10.23
	Median	9.00	8.00	8.00
	SD	7.41	6.54	7.01
	MIN,MAX	1.0,43.0	1.0,41.0	1.0,43.0
	Q1,Q3	5.0,14.0	5.0,13.0	5.0,13.1
	n	176	164	340
	Nmiss	47	62	109

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.1 CRP - Visit 6 (36 Weeks) (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
CRP - V6 (mg/L)	Mean	9.20	7.47	8.36
	Median	7.00	6.00	6.30
	SD	7.10	4.62	6.08
	MIN,MAX	1.0,51.3	1.0,29.0	1.0,51.3
	Q1,Q3	5.0,12.0	4.3,10.0	5.0,11.0
	n	150	140	290
	Nmiss	73	86	159

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.1 Total Cholesterol - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Total Cholesterol - V3 (mmol/L)	Mean	4.87	4.88	4.87
	Median	5.00	4.90	4.95
	SD	1.15	1.09	1.12
	MIN,MAX	2.0,8.3	1.8,8.2	1.8,8.3
	Q1,Q3	4.2,5.7	4.1,5.5	4.1,5.6
	n	216	214	430
	Nmiss	7	12	19
Total Cholesterol - V6 (mmol/L)	Mean	6.32	6.33	6.32
	Median	6.40	6.40	6.40
	SD	1.44	1.74	1.59
	MIN,MAX	2.5,10.5	2.6,12.7	2.5,12.7
	Q1,Q3	5.5,7.3	5.5,7.3	5.5,7.3
	n	144	139	283
	Nmiss	79	87	166

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.2 HDL - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
HDL - V3 (mmol/L)	Mean	1.67	1.64	1.66
	Median	1.60	1.60	1.60
	SD	0.39	0.38	0.38
	MIN,MAX	0.9,3.6	0.0,3.2	0.0,3.6
	Q1,Q3	1.4,1.9	1.4,1.9	1.4,1.9
	n	215	214	429
	Nmiss	8	12	20
HDL - V6 (mmol/L)	Mean	1.70	1.76	1.73
	Median	1.70	1.71	1.70
	SD	0.38	0.43	0.41
	MIN,MAX	0.0,2.9	0.8,3.7	0.0,3.7
	Q1,Q3	1.4,1.9	1.5,2.0	1.4,2.0
	n	145	138	283
	Nmiss	78	88	166

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.3 LDL - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
LDL - V3 (mmol/L)	Mean	2.91	2.89	2.90
	Median	2.84	2.81	2.81
	SD	0.78	0.86	0.82
	MIN,MAX	1.1,5.1	0.0,6.0	0.0,6.0
	Q1,Q3	2.3,3.5	2.3,3.4	2.3,3.4
	n	194	191	385
	Nmiss	29	35	64
LDL - V6 (mmol/L)	Mean	3.57	3.77	3.67
	Median	3.50	3.60	3.60
	SD	1.13	1.25	1.19
	MIN,MAX	0.0,6.8	1.8,9.2	0.0,9.2
	Q1,Q3	2.8,4.3	2.9,4.4	2.8,4.4
	n	126	118	244
	Nmiss	97	108	205

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.4 Triglycerides - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Triglycerides - V3 (mmol/L)	Mean	1.51	1.43	1.47
	Median	1.40	1.30	1.40
	SD	0.53	0.56	0.55
	MIN,MAX	0.5,4.0	0.5,3.7	0.5,4.0
	Q1,Q3	1.1,1.8	1.0,1.6	1.1,1.8
	n	216	214	430
	Nmiss	7	12	19
Triglycerides - V6 (mmol/L)	Mean	2.79	2.76	2.77
	Median	2.70	2.69	2.70
	SD	0.84	0.88	0.86
	MIN,MAX	0.9,5.8	1.3,6.7	0.9,6.7
	Q1,Q3	2.1,3.3	2.1,3.2	2.1,3.2
	n	146	140	286
	Nmiss	77	86	163

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.3 CRP, Cholesterol, HDL, LDL and Triglycerides - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
CRP_log_Visit6 - itt	2.023	0.0931	150	1.872	0.0879	140	-0.151	-0.297	-0.005	4.118	0.0434
Cholesterol_log_Visit6 - itt	1.780	0.0321	144	1.784	0.0302	139	0.004	-0.047	0.055	0.025	0.8751
HDL_Visit6# - itt	1.770	0.0576	145	1.821	0.0544	138	0.051	-0.040	0.142	1.206	0.2730
LDL_log_Visit6$ - itt	1.160	0.0548	125	1.221	0.0508	118	0.062	-0.018	0.141	2.346	0.1270
Triglycerides_log_Visit6 - itt	0.968	0.0439	146	0.960	0.0413	140	-0.007	-0.077	0.062	0.045	0.8327

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Summary statistics are presented in tables 8.1 to 8.2 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted mean of the non-transformed or log transformed variable by allocated treatment,
SE represents standard error of the estimated means or log transfomed means and N represents number of observations
*Represents the difference between the estimated means or log transfomed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_4_other_labs_analysis_v6.lst'
#NOTE:HDL was not log transformed for the analysis
$NOTE:LDL has a value of 0 for patient 16052, this values was set to missing in the log transformation of the parameter
All parameters shown normal or near-normal behavior

Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.1 Glucose and Insuling in the umbilical cord - Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Glucose Cord - V8 (mmol/L)	Mean	3.89	4.06	3.97
	Median	3.70	3.80	3.80
	SD	1.24	1.08	1.16
	MIN,MAX	1.4,7.6	1.6,7.0	1.4,7.6
	Q1,Q3	3.0,4.6	3.2,4.9	3.1,4.8
	n	79	74	153
	Nmiss	144	152	296
Insulin Cord - V8 (mIU/ml)	Mean	10.95	11.41	11.20
	Median	9.89	9.26	9.45
	SD	7.49	8.80	8.20
	MIN,MAX	2.0,32.7	2.0,42.9	2.0,42.9
	Q1,Q3	5.6,14.4	5.2,16.3	5.3,15.2
	n	47	57	104
	Nmiss	176	169	345

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.2 HOMA-IR AND CRP in the umbilical cord - Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
HOMA-IR Cord - V8 (mIU/ml)	Mean	1.92	1.91	1.91
	Median	1.81	1.48	1.59
	SD	1.39	2.00	1.72
	MIN,MAX	0.3,6.7	0.2,12.0	0.2,12.0
	Q1,Q3	0.9,2.3	0.7,2.6	0.7,2.5
	n	38	41	79
	Nmiss	185	185	370
CRP - V8 (mmol/L)	Mean	4.32	2.36	3.37
	Median	1.00	1.00	1.00
	SD	19.55	2.29	14.13
	MIN,MAX	0.1,173.8	0.2,11.0	0.1,173.8
	Q1,Q3	1.0,5.0	1.0,5.0	1.0,5.0
	n	78	73	151
	Nmiss	145	153	298

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.3 Glucose, Insuling and HOMA-IR in the umbilical cord - Visit 8 (Delivery) - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Glucose_cord_log_Visit_8* - itt	1.243	0.0550	79	1.308	0.0513	74	0.065	-0.027	0.157	1.961	0.1637
Insulin_cord_log_Visit_8* - itt	1.992	0.1884	47	2.050	0.1654	57	0.058	-0.265	0.381	0.127	0.7220
HOMA_cord_log_Visit_8* - itt	0.141	0.2009	38	0.154	0.1756	41	0.012	-0.355	0.380	0.004	0.9473

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in tables 9.1 to 9.2 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_9_1_Neonatal_cord_blood.lst'
All parameters shown normal or near-normal behavior

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DOI: 10.3310/eme03070

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Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.4 CRP in the umbilical cord - Visit 8 (Delivery)* - Statistical Analysis - POST-HOC

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Parameter(s)	*Studied effects*	*P-value Wilcoxon Test (Two-sided)*	*P-value Wilcoxon t Approx (Two-sided)*	*P-value Kruskal-Wallis Test*
CRP_CORD_VISIT_8_itt	Non_parametric_test_metformin_vs_placebo*	0.7411	0.7416	0.7411

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician

Summary statistics are presented in table 9.2 of this report

*This variable was non-normal and the lack of normality could not be corrected. Therefore Non-parametric testing results are presented. Significance level set at p<0.05

Calculations and detailed analysis are presented in study file 'Empowar_9_1_Neonatal_cord_blood.lst'

Section 10. Adverse Outcome

10.1.1 Maternal Complications - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any SAE (n)#	Missing	1	4	5
	Yes	45 (20.3)	45 (20.3)	90 (20.3)
	No	177 (79.7)	177 (79.7)	354 (79.7)
Any Hypertension (n)	Missing	1	5	6
	Yes	14 (6.3)	21 (9.5)	35 (7.9)
	No	208 (93.7)	200 (90.5)	408 (92.1)
Any Preeclampsia (n)	Missing	1	5	6
	Yes	3 (1.4)	7 (3.2)	10 (2.3)
	No	219 (98.6)	214 (96.8)	433 (97.7)
Any Eclampsia (n)	Missing	1	5	6
	Yes	1 (0.5)	1 (0.5)	2 (0.5)
	No	221 (99.5)	220 (99.5)	441 (99.5)
Any MembraneRupture (n)	Missing	1	5	6
	Yes	6 (2.7)	5 (2.3)	11 (2.5)
	No	216 (97.3)	216 (97.7)	432 (97.5)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26 By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = number of observations

#This value comes from the 'CRF - Complications' and it is different from the value presented in 13.1.1.1 that comes from 'SAE form'

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DOI: 10.3310/eme03070

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Section 10. Adverse Outcome

10.1.1 Maternal Complications - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any PretermLabour (n)#	Missing	1	5	6
	Yes	6 (2.7)	13 (5.9)	19 (4.3)
	No	216 (97.3)	208 (94.1)	424 (95.7)
Any Haemorrhage (n)	Missing	1	5	6
	Yes	12 (5.4)	8 (3.6)	20 (4.5)
	No	210 (94.6)	213 (96.4)	423 (95.5)
Any DVT (n)	Missing	1	5	6
	Yes	3 (1.4)	2 (0.9)	5 (1.1)
	No	219 (98.6)	219 (99.1)	438 (98.9)
Any Gestational Diabetes (n)	Missing	1	5	6
	Yes	29 (13.1)	22 (10.0)	51 (11.5)
	No	193 (86.9)	199 (90.0)	392 (88.5)

N = number of patients randomised, n = number of observations

#This value comes from the 'CRF - Complications' and it is different from the value presented in 4.1.1.1 that comes from 'CRF - delivery'

Section 10. Adverse Outcome

10.1.1 Maternal Complications - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Parameter(s)	*Categories*	*---------Allocated_Intervention---------* *Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Other Mother Complication (n)	Missing	1	4	5
	Yes	62 (27.9)	65 (29.3)	127 (28.6)
	No	160 (72.1)	157 (70.7)	317 (71.4)
Any Other Mother Complication cat* (n)	Missing	0	1	1
	Infection	20	15	35
	Mood disturbance	4	6	10
	Musculoskeletal	12	16	28
	PV bleed <24 weeks gestation	5	5	10
	Obstetric cholestasis	9	5	14
	Miscellaneous	22	23	45
	Data captured elsewhere	43	38	81

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26

By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = number of observations

*A single patient could have had more than one complication

The complications were categorised by the study team

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DOI: 10.3310/eme03070

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Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
11136	METFORMIN	Yes	VISIT 8 (DELIVERY)	placental abruption
11315	METFORMIN	Yes	VISIT 8 (DELIVERY)	3rd degree tear
11317	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	cerebral venous sinus thrombosis
11317	METFORMIN	Yes	VISIT 8 (DELIVERY)	cerebral sinus thrombosis
11325	METFORMIN	Yes	VISIT 5 (28 WEEKS)	antenatal depression
11501	METFORMIN	Yes	VISIT 6 (36 WEEKS)	hospital admission with RUQ pain and deranged LFT, resolved spontaneously
11551	METFORMIN	Yes	VISIT 5 (28 WEEKS)	exacerbation of asthma requiring oral steroids
11657	METFORMIN	Yes	VISIT 5 (28 WEEKS)	UTI early pregnancy. Also just completed antibiotics and steroids for chest infection
11657	METFORMIN	Yes	VISIT 8 (DELIVERY)	Increased liquor volume
11686	METFORMIN	Yes	VISIT 8 (DELIVERY)	Breast cancer
11716	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Mild SPD
11748	METFORMIN	Yes	VISIT 6 (36 WEEKS)	UTI
11748	METFORMIN	Yes	VISIT 7 (TERM)	Sepsis secondary to mastitis
11748	METFORMIN	Yes	VISIT 8 (DELIVERY)	UTI SAE forms previously sent
11797	METFORMIN	Yes	VISIT 6 (36 WEEKS)	excessive vomiting in late pregnancy
11842	METFORMIN	Yes	VISIT 8 (DELIVERY)	Raised ALT
11881	METFORMIN	Yes	VISIT 8 (DELIVERY)	severe urosepsis
11916	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	contacted Lucy who reported she has been in hospital with kidney infection and was on abx. No note in electronic medical record.
12001	METFORMIN	Yes	VISIT 7 (TERM)	Sweling of hands and feet
12001	METFORMIN	Yes	VISIT 8 (DELIVERY)	oedema
12008	METFORMIN	Yes	VISIT 8 (DELIVERY)	Post Partum haemorrhage, 2000ml
12018	METFORMIN	Yes	VISIT 8 (DELIVERY)	EBL 600 mls
12099	METFORMIN	Yes	VISIT 8 (DELIVERY)	3rd degree tear,
13016	METFORMIN	Yes	VISIT 7 (TERM)	Seen in assessment room last week with headache and visual disturbances. Migrane diagnosed. Discharged home with paracetamol and codine.
13047	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	After a week of medication, reports severe vomitting and diarrheoa, lasting a week. Has been off work for a week, doesn't wish to reccomence drugs.
13047	METFORMIN	Yes	VISIT 8 (DELIVERY)	IOL FOR FACTOR 5 LEIDENS
13082	METFORMIN	Yes	VISIT 8 (DELIVERY)	PYREXIA IN LABOUR
13111	METFORMIN	Yes	VISIT 8 (DELIVERY)	IOL FOR CHOLESTASIS ALSO HAD GESTATIONAL DIABETES, COMMENCED ON METFORMIN BY DIABETES TEAM AT 30WEEKS. TOOK METFORMIN 1,000MG BD UNTILL DELIVERY. ALSO COMMENCED ON INSULIN FROM 31WKS.
13147	METFORMIN	Yes	VISIT 6 (36 WEEKS)	cervical bleeds frequently throughout pregnancy. no addmissions.
13209	METFORMIN	Yes	VISIT 6 (36 WEEKS)	HAD VIRAL INFECTION 2 WEEKS AGO LASTING A FORTNIGHT. RESULTED IN PRODUCTIVE COUGH, FOLLOWED MODERATE VOMITTING AND DIARROHEA.
13248	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	ADMITTED TO WARD VIA EMERGENCY ROOM FOR ABDO PAIN, DISCHARGED AFTER 2DAYS, DIAGNOSIS - IBS.
13305	METFORMIN	Yes	VISIT 6 (36 WEEKS)	SPD PAIN. ON COCODAMOL.
13378	METFORMIN	Yes	VISIT 5 (28 WEEKS)	UTI CAUSED SEVERE HEADACHES. CLEARED AFTER COURSE OF ANTIBIOTICS.
13378	METFORMIN	Yes	VISIT 8 (DELIVERY)	Fatty deposits noted on placenta, samples taken for histology by delivery midwife, but enable to process as incorrectly sampled and stored
13493	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Attended A+E for feeling dizzy, palipitations, breathless and tight chest. Reports ECG and all investigations found to be normal. No treatment or follow up required. Discussed with Dr Weeks and advised doesn't meet criteria of SAE, hospitakisation was for <12 hours

Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
13551	METFORMIN	Yes	VISIT 8 (DELIVERY)	PPH of 5000ml followed by total hysterectomy
13780	METFORMIN	Yes	VISIT 8 (DELIVERY)	UNDIAGNOSED LOW LYING PLACENTA AT CS. BLOOD LOSS 1400MLS. NEEDED BLOOD TRANSFUSION AFTER CS.
14035	METFORMIN	Yes	VISIT 6 (36 WEEKS)	ALT result from today 95IU/L.No symptoms of PET/HELPP or Obstetric Cholestasis
14035	METFORMIN	Yes	VISIT 8 (DELIVERY)	Induced due to upper right abdominal and increased LFT's ? cause
14039	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Has had x1 episode of PV bleeding and mild abdominal pain @ 30+4. Admitted overnight, no further PV Loss. Also had viral illness 1 week ago, no treatment.
14039	METFORMIN	Yes	VISIT 7 (TERM)	B/P Slightly elevated. One episode of PV spotting
14039	METFORMIN	Yes	VISIT 8 (DELIVERY)	Pregnancy Induced Hypertension
14161	METFORMIN	Yes	VISIT 8 (DELIVERY)	PPH 1500ml
14303	METFORMIN	Yes	VISIT 8 (DELIVERY)	PPH 1200mls
14305	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Maternal UTI
14417	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Feeling faint on occasions when working
15012	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	has had small pv bleed as history of cervical polyps all well
15027	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Itching All blood tests NAD
16029	METFORMIN	Yes	VISIT 6 (36 WEEKS)	abdo pain ?SPD (admission) plus triage assessment for reduced fetal movements
16029	METFORMIN	Yes	VISIT 7 (TERM)	Abdo pain admission on 03.09.2012 (SAE) plus Raised ALT on 3 occasions ?obstetric choleostatsis asymptomatic
16029	METFORMIN	Yes	VISIT 8 (DELIVERY)	Abdo pain (SAE) plus raised ALT, IOL for Obstetric Choleostasis
16054	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Abdo pain and pinkish pv loss
16121	METFORMIN	Yes	VISIT 6 (36 WEEKS)	pyelonephritis
17138	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Palpitations, seen in hospital assessment unit but discharged home without admission. Normal ECG and Normal CTG.
21015	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Attended Day Unit 4/9/13 33+4 with brown pv discharge post coital.
21015	METFORMIN	Yes	VISIT 7 (TERM)	Questions asked in retrospect once delivered as unable to contact.Unsure when stopped tablets.
21015	METFORMIN	Yes	VISIT 8 (DELIVERY)	PPH following birth.Hb 63g/l.Had 2 units of blood.Hb 83g/l post transfusion.Didnt cause prolonged hospitalisation.
21034	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Indigestion since 22 weeks resolved with use of gaviscon
21034	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Acupuncture for back/hip pain. Broke coccyx 5 years ago
21037	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Sweating
21037	METFORMIN	Yes	VISIT 7 (TERM)	Green vaginal discharge today High vaginal swab obtained.
21039	METFORMIN	Yes	VISIT 8 (DELIVERY)	Maternal tachycardia post delivery. IV fluids & antibiotics given. Ragged membranes.
21042	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Heartburn. Using gaviscon. Awaiting precription of ranitidine
21042	METFORMIN	Yes	VISIT 5 (28 WEEKS)	07/09/2013 self referral to maty ward feeling dizzy. 21/09/2013 ?SROM HVS showed Group B Strep. On last day of Amoxycillin treatment today.Gestational diabetes today. Attending for glucometer tomorrow
21042	METFORMIN	Yes	VISIT 7 (TERM)	Group B Strep diagnosed in pregnancy.
21042	METFORMIN	Yes	VISIT 8 (DELIVERY)	Induction of labour for gestational diabetes. Group B Strep identified in pregnancy.
21064	METFORMIN	Yes	VISIT 5 (28 WEEKS)	UTI 21/10/13 cephalexin tds for 5 days taken.
21064	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Right sided abdo pain on 2 occasions 15 & 22/11/13 been fine since.
21064	METFORMIN	Yes	VISIT 8 (DELIVERY)	SPD
21070	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Lower backache has appt with physio on 8/10/13

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DOI: 10.3310/eme03070 EFFICACY AND MECHANISM EVALUATION 2016 VOL. 3 NO. 7

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Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
21070	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Symphisis Pubis Disfunction-physio input
21070	METFORMIN	Yes	VISIT 6 (36 WEEKS)	SPD
21070	METFORMIN	Yes	VISIT 8 (DELIVERY)	SPD-S/B Physio & had acupuncture.
21074	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Backache 16+ weeks saw GP & resolved a few days later
21074	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Wort on finger.
21074	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Itching on legs, had same prior to pregnancy. Wort on finger.
21074	METFORMIN	Yes	VISIT 7 (TERM)	03/02/14 headache for 24 hours.Started on antibiotics as ?UTI. Normal MSSU so stopped taking. Only took 1 tablet.
21074	METFORMIN	Yes	VISIT 8 (DELIVERY)	26/2/14 perineal infection flucloycillin commenced orally at home.
21081	METFORMIN	Yes	VISIT 7 (TERM)	Taking fluoxetine for depression.
21081	METFORMIN	Yes	VISIT 8 (DELIVERY)	On fluoxetine.
21082	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	20/10/13 attended primary care/gynae feeling unwell ?food poisoning/palpatations normal investigations.Some low mood/depression.
21082	METFORMIN	Yes	VISIT 6 (36 WEEKS)	3/1/14 29+4 episode of raised BP settled. 30/1/14 33+3 antibiotics for UTI.
21082	METFORMIN	Yes	VISIT 7 (TERM)	Some hypertension-settled now.
21082	METFORMIN	Yes	VISIT 8 (DELIVERY)	Pyrexial in labour/maternal tachycardia. IV paracetamol required.
21089	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Several symptoms feels were associated with tablet use, therefore stopped taking. Last dose taken 25/10/13.
21089	METFORMIN	Yes	VISIT 7 (TERM)	Admission to maternity Ward with hypermesis for over 12 hours.
21089	METFORMIN	Yes	VISIT 8 (DELIVERY)	Anaemic post delivery. Taking ferrous sulphate tablets.
21095	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Started citalopram for depression on 04/11/13.
21095	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Lower back discomfort sees physio.
21095	METFORMIN	Yes	VISIT 8 (DELIVERY)	On citalopram for depression
21099	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Tooth abcess so had to reduce tablets one day.
21099	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Eleveated BP today for close monitoring. Occasionally takes Co-dydramol for backache. Physio/acupuncture unsucessful.
21099	METFORMIN	Yes	VISIT 8 (DELIVERY)	Raised blood pressure
21111	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Small pv bleed 08/12/13 19+ weeks. Investigations NAD. Not admitted to Gynae.
21111	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Upper abdominal discomfort for 4-5 weeks on and off.
21111	METFORMIN	Yes	VISIT 7 (TERM)	Amoxycillin 500mgs TDS for suspected chest infection.
21125	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Occasional light headedness. Normal Hb.
21127	METFORMIN	Yes	VISIT 5 (28 WEEKS)	SPD on crutches seeing physio.
21127	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Seeing physio & having acupuncture for hip pain.
21127	METFORMIN	Yes	VISIT 8 (DELIVERY)	SPD/Hip pain. Has seen physio/had crutches/acupuncture.
21128	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Backache & sciatica
21128	METFORMIN	Yes	VISIT 8 (DELIVERY)	Postpartum haemorrhage.
25180	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Two separate overnight admissions mid June first time with ?pyelonephritis and second time with pain ?due to gall-stones found at time on ultrasound scan
25264	METFORMIN	Yes	VISIT 5 (28 WEEKS)	obstetric cholestasis
25382	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	diarrhoea

Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
25459	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Right Adrexal ovarian cyst
25459	METFORMIN	Yes	VISIT 8 (DELIVERY)	Induction of labour due to pain from known ovarian cyst
27317	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	stomach cramps & backache.
53059	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Had contact with nephew with chicken pox and does not have immunity. Therefore had to attend for immunoglobulin
11081	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	on going hyperemesis requiring antiemetic (predates trial)
11262	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Borderline raised ALT
11262	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Raised ALT, probable obstetric cholestasis but advised to stop treatment for 2 weeks and then we will repeat ALT
11262	PLACEBO	Yes	VISIT 6 (36 WEEKS)	obstetric cholestasis
11262	PLACEBO	Yes	VISIT 8 (DELIVERY)	obstetric cholestasis
11263	PLACEBO	Yes	VISIT 6 (36 WEEKS)	APH-admitted for 24 hours at 34 weeks gestation following minimal PVB. No cause found
11263	PLACEBO	Yes	VISIT 8 (DELIVERY)	PPH
11323	PLACEBO	Yes	VISIT 8 (DELIVERY)	3rd degree tear (3a)
11397	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	occasional mild palpitations, experienced this in previous pregnancy
11411	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	aware of palpitations
11443	PLACEBO	Yes	VISIT 6 (36 WEEKS)	itch-possible obstetric cholestasis
11643	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Hospitalised for abdominal pain at 25 weeks, found to have c. diff. Treated for this and then experienced very painful haemorrhoids. Stopped taking study medication, but happy to continue with GTT and other data collection.
11693	PLACEBO	Yes	VISIT 8 (DELIVERY)	Obstetric cholestasis
11725	PLACEBO	Yes	VISIT 7 (TERM)	SPD
11940	PLACEBO	Yes	VISIT 6 (36 WEEKS)	currently on prednisolone for chest infection
11940	PLACEBO	Yes	VISIT 8 (DELIVERY)	Hospitalised due to chest infection.
12019	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Thrush
12020	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Ear infection/vertigo
12020	PLACEBO	Yes	VISIT 5 (28 WEEKS)	vertigo
12020	PLACEBO	Yes	VISIT 8 (DELIVERY)	PPH 1500 - 2500 mls
12021	PLACEBO	Yes	VISIT 5 (28 WEEKS)	25/04/2012 In triage for UTI. Sent home with trimetheprim.
12065	PLACEBO	Yes	VISIT 8 (DELIVERY)	Diet controlled GDM
12074	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Admitted with pv bleed
12092	PLACEBO	Yes	VISIT 8 (DELIVERY)	Pyrexia. Treated with iv antibiotics.
13007	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Was weepy when increased dose to 4 tablets at week 4. Therefore has decreased to 2 tablets daily. Not having weepiness any longer, suggested trying to increase to TDS, - will try, but not willing to increase dose further. 4/3/11
13015	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	has had hyperemisis since randomisation untill now and not commenced on study medication.
13015	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Hyperemesis from 12-22wks. No hospital addmission. Unable to take study drugs due to sickness.
13058	PLACEBO	Yes	VISIT 6 (36 WEEKS)	vomiting and feeling very unwell migraines increasingly worse
13144	PLACEBO	Yes	VISIT 5 (28 WEEKS)	SYMPHISIS PUBIS DISORDER
13144	PLACEBO	Yes	VISIT 7 (TERM)	Has had fainting episodes for past 6 weeks. Now has IOL booked for 38wks due to this. Reports has had several addmissions with raised blood pressure and protien urea.
13144	PLACEBO	Yes	VISIT 8 (DELIVERY)	Reported frequent fainting episodes. not investigated, occassional episodes of raised BP, BP profile NAD. IOL on request in view of repeaded fainting.

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DOI: 10.3310/eme03070

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Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
13217	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Hip pain due to looseness in joint. Under physio. Not on medication.
13217	PLACEBO	Yes	VISIT 8 (DELIVERY)	PPH, HAD OXYTOCIC DRUGS
13301	PLACEBO	Yes	VISIT 5 (28 WEEKS)	HAD COLLAPSE WHEN OUT SHOPPING. ADVISED TO STOP MEDICATION AS GLUCOSE LEVEL WAS REPORTED TO BE LOW WHEN CHECKED AT GP.
13301	PLACEBO	Yes	VISIT 8 (DELIVERY)	Intrapartum haemmorhage and postnatal haemorrhage total = 2000ml
13380	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	14mgs cetalopram seeing pysc assessment.Had already been on this dose before preganancy, but may need to increase.
13504	PLACEBO	Yes	VISIT 8 (DELIVERY)	Prolonged rupture of membranes for 98 hours, sepsis
13591	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Fell on the bus when it stopped suddenly. Had small pv bleed, attended hospital for anti d, but was not admitted and not for any follow up. As reports fall was due to bus stopping suddenly and no episodes of dizziness or feeling faint not an SAE.
13667	PLACEBO	Yes	VISIT 8 (DELIVERY)	IOL FOR SPD PPH 1200ML
13712	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Obstetric Choleostasis
13712	PLACEBO	Yes	VISIT 8 (DELIVERY)	choleostasis
14036	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	PV spotting diagnosed as thrush by GP
14036	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Seen in Triage 11/10/11. C/O Tightenings, Abdominal pain, moderate Symphysis Pubis disfunction. Diagnosed with UTI and given analgesics and antibiotics.
14036	PLACEBO	Yes	VISIT 8 (DELIVERY)	Maternal Post Partum Haemorrhage
14037	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Anaemia taking Ferrous Fumerate BD
14037	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Maternal Obstetric Cholestasis
14037	PLACEBO	Yes	VISIT 8 (DELIVERY)	Induced due to Maternal Obstetric Cholestasis
14061	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Viral Illness
14061	PLACEBO	Yes	VISIT 8 (DELIVERY)	Maternal Intracrannial Hypertension
14089	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Attended Triage 26.04.12 - Abdo pain, D&V. Not admitted. ?Viral gastroenteritis.
14145	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Admitted to Leeds General Infirmary. Reported on 07/09/12
14205	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Double vision. Currently under investigation by eye clinic.
14270	PLACEBO	Yes	VISIT 8 (DELIVERY)	suspected Chorioamniitis.
14272	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Severe headache requiring hospitalistaion and investigation 18.04.13
14336	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Seen by SHO in Triage 13.09.13 re abdominal pain. Now resolved ?viral enteritis
14336	PLACEBO	Yes	VISIT 8 (DELIVERY)	see SAE
14354	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Ovarian cyst on right ovary diagnosed
14354	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Admitted with small APH and tightenings for 5 days - SAE completed 22.12.13
14413	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Abdominal pain 03.10.13 Seen in Early Pregnancy Assessment Centre
15010	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	metallic taste
15010	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Has some itching bile acids nad
15028	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Admitted to assessment centre and for PPROM on 140413 admitted for less than 12hours Seen by Mr Simm consultant who advised Research Midwife. For conservative management at the moment. For further scans on Thursday 18th April. Admitted as inpatient on Thursday 18th April with confirmed prom and oligohydramnious.
15028	PLACEBO	Yes	VISIT 5 (28 WEEKS)	As stated earlier Prem rupture of Membranes
16052	PLACEBO	Yes	VISIT 8 (DELIVERY)	PPH 1800ml
17036	PLACEBO	Yes	VISIT 7 (TERM)	hospital admission as had flu
17036	PLACEBO	Yes	VISIT 8 (DELIVERY)	raised ALT liver scan

Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
17137	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Costochondritis
17137	PLACEBO	Yes	VISIT 8 (DELIVERY)	Costochondritis
21010	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Persistent glycosuria between 28+ and 35+ weeks gestation. Normal GTTs.
21018	PLACEBO	Yes	VISIT 5 (28 WEEKS)	pv bleed before 16 weeks gestation, prior to commencing tablets.Hospitalised for observation discharged within 12 hours.
21018	PLACEBO	Yes	VISIT 6 (36 WEEKS)	4/9/13 32+6 shortness of breath/palpitations. Investigations normal.
21018	PLACEBO	Yes	VISIT 7 (TERM)	Various episodes of reduced fetal movements see on MDCU had CTGs. H/o palpatations normal investigations.
21018	PLACEBO	Yes	VISIT 8 (DELIVERY)	Difficult caesarean section.
21038	PLACEBO	Yes	VISIT 8 (DELIVERY)	Readmitted via ambulance 29/12/13 pv bleed/abdo pain. Stayed in hospital for less than 12 hours. No SAE required.
21044	PLACEBO	Yes	VISIT 6 (36 WEEKS)	pyogenic granuloma on finger of left hand.Had x2 doses of flucloxycillin.UTI cephalexin for 1 week.
21047	PLACEBO	Yes	VISIT 5 (28 WEEKS)	20+4 (3-4/9/13) brief episode in A&E pain from gall stones settled after morphine discharged home after few hours.
21069	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Antibiotics for 1 week for ear infection 05/09/13
21069	PLACEBO	Yes	VISIT 5 (28 WEEKS)	UTI treated with cefalexin.
21069	PLACEBO	Yes	VISIT 8 (DELIVERY)	Sepsis in labour.SAE form completed as prolonged hospitalisation.
21077	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Attended A&E with abdo pain 28/9/13
21077	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Headaches. Community Midwife advised to stop taking tablets on 23/9/13.
21077	PLACEBO	Yes	VISIT 6 (36 WEEKS)	5/12/13 29+2 GP referral c/o headache/oedema/episode of palpitations/?fainting episode. Investigations NAD.
21077	PLACEBO	Yes	VISIT 7 (TERM)	Feeling generally unwell.
21078	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Hb low for oral iron
21078	PLACEBO	Yes	VISIT 6 (36 WEEKS)	16/1/14 episode of reduced fetal movements. CTG NAD.
21078	PLACEBO	Yes	VISIT 7 (TERM)	On ferrous sulphate tablets as anaemic since last visit.
21093	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Small antepartum haemorrhage. Overnight stay on maternity ward for over 12 hours.
21093	PLACEBO	Yes	VISIT 6 (36 WEEKS)	28/12/13 sight pv bleeding no admission. 24/1/14 Antibiotics for bacterial vaginosis & canestan for thrush. 3/2/14 brief isolated episode of raised BP settled on day unit no admission.
21093	PLACEBO	Yes	VISIT 8 (DELIVERY)	Raised BP in labour
21100	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	28/10/13 thrush detected.Prescription off GP.
21100	PLACEBO	Yes	VISIT 6 (36 WEEKS)	UTI on MSSU 17/01/14 treated with cefalexin.
21100	PLACEBO	Yes	VISIT 7 (TERM)	UTI-commenced Trimethroprim BD for 3 days on 31/3/14.
21100	PLACEBO	Yes	VISIT 8 (DELIVERY)	Antepartum haemorrhage 1200mls. Manual removal of placenta & postpartum haemorrhage of 800mls. Blood transfusion.
21109	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Heartburn. Day Unit visit 16/12/13 abdo pain.
21109	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Admitted over 12 hours with UTI. Oral antibiotics/steroids/ferrous sulphate.SAE form completed & faxed to Sponsors.
21109	PLACEBO	Yes	VISIT 7 (TERM)	Admitted for 2 nights on 03/4/14 with lower abdo discomfort, braxton hicks, red pv loss, unstable lie.
21109	PLACEBO	Yes	VISIT 8 (DELIVERY)	Admitted with lower abdo discomfort, red pv loss, Braxton Hicks,unstable lie 03/4/14
21122	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Prolonged nausea.
21122	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Prolonged nausea
21122	PLACEBO	Yes	VISIT 7 (TERM)	Musculoskeletal pain/SPD. Group B Strep positive.
21122	PLACEBO	Yes	VISIT 8 (DELIVERY)	SPD/musculoskeletal pain. Group B Strep positive.

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DOI: 10.3310/eme03070

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Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*Other Maternal Complications (Y/N)*	*TimepointID*	*Other Maternal Complications Details*
21133	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Feels down.
21133	PLACEBO	Yes	VISIT 5 (28 WEEKS)	25/2/14 tonsillitis/viral infection treated with penecillin.
21133	PLACEBO	Yes	VISIT 6 (36 WEEKS)	11/4/14 & 23/5/14 admissions for likely costochondritis.
21133	PLACEBO	Yes	VISIT 7 (TERM)	Symphisis Pubis Dysfunction. Taking Co-Codamol.
21133	PLACEBO	Yes	VISIT 8 (DELIVERY)	SPD. Hypertension in labour.
24035	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	In last 48 hours has suffered with nausea and vomiting; high level stomach pains that radiate down her sides and into her back - above her bra strap; and headache. These symptoms she has had only for last 48 hours..??viral
25100	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	severe headaches on the medication that the P.I. has reported as an SAE, headaches stopped when medication was suspended. P.I has recommended stopping medication completly
25100	PLACEBO	Yes	VISIT 6 (36 WEEKS)	symphius pubis dysfunction requiring a few days of bed rest in hospital
25100	PLACEBO	Yes	VISIT 7 (TERM)	depression, symphius pubis dysfunction
25165	PLACEBO	Yes	VISIT 8 (DELIVERY)	PPH 2.5L
25391	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	brown/green pv loss on 2.11.13. pv spotting on 12.11.13. HVS group B streptococcus.
25391	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Abdominal pain ?cause
25391	PLACEBO	Yes	VISIT 7 (TERM)	depression and musculoskeletal pain
53014	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	has had persistant cough since sept. Has seen own doctor (GP, had course of antibiotics. Also seen at general hospital advised re inhalers and improved with this (as is asthmatic)

Section 10. Adverse Outcome

10.1.3.1 Maternal Complications - Hypertension - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of ANY_HYPER by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
ANY_HYPER	*METFORMIN*	*PLACEBO*	*Total*
Missing	5	1	.
No	200	208	408
Yes	21	14	35
Total	221	222	443

Frequency Missing = 6

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
ANY_HYPER_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.560	0.772	3.152	0.2155	0.2232

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26

By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is ANY_hyper='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_10_1_1_Npatients_hypertension_analysis.lst'

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Section 10. Adverse Outcome

10.1.3.2 Maternal Complications - Preeclampsia - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of ANY_Preecla by AllocatedTreatment*

	AllocatedTreatment(Allocated Treatment)		
ANY_Preecla	*METFORMIN*	*PLACEBO*	*Total*
Missing	5	1	.
No	214	219	433
Yes	7	3	10
Total	221	222	443

Frequency Missing = 6

Parameter(s)	*Studied effects*		*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
ANY_Preecla_itt	AllocatedTreatment	METFORMIN vs PLACEBO	2.388	0.609	9.355	0.2116	0.2207

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26

By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is ANY_preecla='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_10_1_1_Npatients_preeclamp_analysis.lst'

Section 10. Adverse Outcome

10.2.1 Fetal Complications* - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Fetal Complication (n)	Missing	1	5	6
	Yes	47 (21.2)	43 (19.5)	90 (20.3)
	No	175 (78.8)	178 (80.5)	353 (79.7)
Fetal AC (n)	Missing	221	226	447
	No	2	0	2
Fetal Liquor (n)	Missing	158	173	331
	Yes	6	3	9
	No	59	50	109
Fetal Doppler (n)	Missing	159	174	333
	Yes	0	1	1
	No	64	51	115
Fetal Absent EDF (n)	Missing	160	175	335
	Yes	2	0	2
	No	61	51	112

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26
N = number of patients randomised, n = number of observations
*A single patient could have had more than one complication

By: Aryelly Rodriguez - ECTU Statistician

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Section 10. Adverse Outcome

10.2.1 Fetal Complications* - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)(Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Fetal Reverse EDF (n)	Missing	160	175	335
	No	63	51	114
Fetal Abnormal CTG (n)	Missing	157	175	332
	Yes	14	11	25
	No	52	40	92
Other Fetal Complication (n)	Missing	152	159	311
	Yes	32	35	67
	No	39	32	71
Other Fetal Complication cat#(n)	Data captured elsewhere	19	22	41
	Meconium stained liquor	4	5	9
	Miscellanous	2	3	5
	Polyhydramnios	3	3	6
	Reduced fetal movements	7	10	17
	Shoulder dystocia	2	0	2

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26

By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = number of observations

*A single patient could have had more than one complication

#The complications were categorised by the study team

Section 10. Adverse Outcome

10.2.2 Fetal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Fetal Complications Other (Y/N)	TimepointID	Fetal Complications Other Details
11078	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	abnormal anomaly scan - probable CCAM
11078	METFORMIN	Yes	VISIT 6 (36 WEEKS)	USS 26/10/11: large left sided CCAM with mediastinal shift.
11078	METFORMIN	Yes	VISIT 8 (DELIVERY)	baby known antenatally to have CCAM
11557	METFORMIN	Yes	VISIT 8 (DELIVERY)	reduced fetal movements and clinically felt to be small for dates although growth scan normal
11566	METFORMIN	Yes	VISIT 8 (DELIVERY)	Baby required resuscitation at delivery
11880	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	unknown cause of IUD detected at FAS
11880	METFORMIN	Yes	VISIT 8 (DELIVERY)	Fetal death diagnosed at 20 weeks
12001	METFORMIN	Yes	VISIT 8 (DELIVERY)	macrosomia
12006	METFORMIN	Yes	VISIT 8 (DELIVERY)	confirmed IUD on 10/02/2012
12018	METFORMIN	Yes	VISIT 6 (36 WEEKS)	scan at 36 weeks shows abdominal circumstance static,attending further scan in one week
12034	METFORMIN	Yes	VISIT 8 (DELIVERY)	Premature delivery.
12055	METFORMIN	Yes	VISIT 8 (DELIVERY)	IUGR
12056	METFORMIN	Yes	VISIT 8 (DELIVERY)	fetal abnormaility known fetal hydrops
13508	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	18/40 spontaneous misscarriage
13551	METFORMIN	Yes	VISIT 8 (DELIVERY)	Low Cord PH's on FBS
14131	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Renal pelivis Left kidney dliated
14162	METFORMIN	Yes	VISIT 8 (DELIVERY)	Reduced fetal Movements
14203	METFORMIN	Yes	VISIT 8 (DELIVERY)	Raised doppler on 07.01.13
14303	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Polyhydramnios
15003	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Breech presentation
16029	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Mesenterial Cyst
16029	METFORMIN	Yes	VISIT 8 (DELIVERY)	Reduced fetal movements
16064	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Reduced fetal movements x 2 days
16121	METFORMIN	Yes	VISIT 7 (TERM)	Persistent reduced fetal movements
16121	METFORMIN	Yes	VISIT 8 (DELIVERY)	Persistent reduced fetal movements
16133	METFORMIN	Yes	VISIT 7 (TERM)	polyhydramnios
16133	METFORMIN	Yes	VISIT 8 (DELIVERY)	polyhydramnios
17047	METFORMIN	Yes	VISIT 8 (DELIVERY)	Meconium liquor
21042	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Episodes of reduced fetal movements.
21070	METFORMIN	Yes	VISIT 8 (DELIVERY)	Thick meconium liquor on SROM.
21074	METFORMIN	Yes	VISIT 6 (36 WEEKS)	x1 episode of no fetal movements 25/11/13 28+5. Normal CTG.
21074	METFORMIN	Yes	VISIT 7 (TERM)	Reduced fetal movements 03/02/14. Normal scan.
21081	METFORMIN	Yes	VISIT 7 (TERM)	Episiode of reduced fetal movements.
21082	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Growth below lower centile.
21082	METFORMIN	Yes	VISIT 8 (DELIVERY)	Thick meconium liquor. Fetal tachycardia in labour.
21095	METFORMIN	Yes	VISIT 8 (DELIVERY)	Meconium liquor

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Section 10. Adverse Outcome

10.2.2 Fetal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Fetal Complications Other (Y/N)	TimepointID	Fetal Complications Other Details
21125	METFORMIN	Yes	VISIT 8 (DELIVERY)	Lightly stained meconium liquor.
21127	METFORMIN	Yes	VISIT 8 (DELIVERY)	Growth on 10th centile.
21128	METFORMIN	Yes	VISIT 8 (DELIVERY)	IUGR. Growth on lower centile. Double knot in cord.
25180	METFORMIN	Yes	VISIT 8 (DELIVERY)	mildly dilated lateral ventricular horns on postnatal cephalic USS
25226	METFORMIN	Yes	VISIT 8 (DELIVERY)	Baby had IVABX as prev NND for Group B Strep and EColi.
25459	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Anomoly scan show right unilateral talipes
53059	METFORMIN	Yes	VISIT 6 (36 WEEKS)	HAD 2X GROWTH USS FOR ?IUGR. SECOND USS SHOWED NORMAL GROWTH.
11295	PLACEBO	Yes	VISIT 8 (DELIVERY)	cardiac abnormality as previously reported
11386	PLACEBO	Yes	VISIT 8 (DELIVERY)	shoulder dystocia, relieved with McRoberts and suprapubic pressure, Apgars 8 and 9
11564	PLACEBO	Yes	VISIT 8 (DELIVERY)	baby required resuscitation at delivery
11632	PLACEBO	Yes	VISIT 8 (DELIVERY)	Suspected IUGR
12020	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Reduced fetal movements
12021	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Polyhydramnios
12021	PLACEBO	Yes	VISIT 6 (36 WEEKS)	po;yhydramnios detected on scan at 28+4 weeks. Large for getational age detected at 34+2 weeks.
12030	PLACEBO	Yes	VISIT 5 (28 WEEKS)	amniotic band noted at 20/40 repeat scan done NAD
12038	PLACEBO	Yes	VISIT 6 (36 WEEKS)	? iugr on uss
13301	PLACEBO	Yes	VISIT 8 (DELIVERY)	Undiagnosed oblique breech lie, intrapartum haemorrhage
13473	PLACEBO	Yes	VISIT 8 (DELIVERY)	Baby admitted to NICU for low BM's for 24 hours. No IV fluids required, baby tube fed only. Lowest BM 1.7mmol. Now maintaining BM's and back on postnatal ward with mum
13504	PLACEBO	Yes	VISIT 8 (DELIVERY)	Baby born in poor condition at birth, intubated and respiratory effort not achieved until 8 minutes of age, admitted to NICU for sceptic screen
13591	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Raised growth on USS, at 32/40 and 35/40 measurments >95th centile. EFW at 35/40 3456g
13591	PLACEBO	Yes	VISIT 8 (DELIVERY)	Suspected fetal macrosomia
14061	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Reduced fetal movements. Growth scan performed AC on 5th centile shown. Repeat in 2 weeks. Scan 07/11/2011 Showed nomal growth and normal fetal movements.
14061	PLACEBO	Yes	VISIT 8 (DELIVERY)	Maternal reporting of reduced fetal mevements. FM's seen on USS
14145	PLACEBO	Yes	VISIT 5 (28 WEEKS)	On USS Fetus has transpostion of the great arteries, a ventricular septal defect and ?coartation of the aorta.
14145	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Fetal Abdominal Circumference on 97th centile. AFI increased (19cm)
14264	PLACEBO	Yes	VISIT 8 (DELIVERY)	Intermittently absent EDF
15010	PLACEBO	Yes	VISIT 5 (28 WEEKS)	one episode of reduced fetal movements ctg monitoring normal
15028	PLACEBO	Yes	VISIT 5 (28 WEEKS)	oligohydramnious
16053	PLACEBO	Yes	VISIT 8 (DELIVERY)	shoulder dystocia
16126	PLACEBO	Yes	VISIT 8 (DELIVERY)	Reduced fetal movements x3 episodes
18114	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Measuring Large for Dates. Head circumference and abdominal circumference above 95th centile.
21018	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Polyhydramnious on uss 8/8/13 (29 weeks) & 21/8/13 (30+6 weeks) has since resolved. Reduced fetal movements had monitoring on x4 occasions & again today.
21038	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Growth on lower centile today. Normal doppler
21069	PLACEBO	Yes	VISIT 8 (DELIVERY)	Thick meconium stained liquor during labour.
21077	PLACEBO	Yes	VISIT 8 (DELIVERY)	Meconium liquor
21093	PLACEBO	Yes	VISIT 6 (36 WEEKS)	27/1/14 growth on lower centile. 03/2/14 mild polyhyrdamnious. 10/2/14 normal growth & liquor volume.

Section 10. Adverse Outcome

10.2.2 Fetal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*Fetal Complications Other (Y/N)*	*TimepointID*	*Fetal Complications Other Details*
21093	PLACEBO	Yes	VISIT 8 (DELIVERY)	Light, thin meconium liquor
21109	PLACEBO	Yes	VISIT 6 (36 WEEKS)	21/02/2014 uss normal growth. Liquor volume just above upper centile.
21119	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Fetal abnormality on anomaly ultrasound scan.
25034	PLACEBO	Yes	VISIT 8 (DELIVERY)	meconium stained liquor
25100	PLACEBO	Yes	VISIT 7 (TERM)	one episode of reduced fetal movement
25165	PLACEBO	Yes	VISIT 8 (DELIVERY)	PROM 66 hours
25320	PLACEBO	Yes	VISIT 8 (DELIVERY)	baby's scan on the 30/1/2014 continued to show baby had a full stomach. suspected Hirschsprungs disease in neonate.
25364	PLACEBO	Yes	VISIT 7 (TERM)	Large for dates on scan

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Section 11. Neonatal Care - All Patients

11.1 Neonatal Care

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Care after delivery (n(%))	Missing	3	11	14
	Normal Care	185 (84.1)	196 (91.2)	381 (87.6)
	Special Care	14 (6.4)	7 (3.3)	21 (4.8)
	Level 2 intensive care (ie high dependency intensive care)	9 (4.1)	6 (2.8)	15 (3.4)
	Level 1 intensive care (maximal intensive care)	6 (2.7)	1 (0.5)	7 (1.6)
	Other	6 (2.7)	5 (2.3)	11 (2.5)
Any Congenital Abnormality (n(%))	Missing	5	15	20
	Yes	9 (4.1)	8 (3.8)	17 (4.0)
	No	209 (95.9)	203 (96.2)	412 (96.0)
Other Hospital Admission (n(%))	Missing	18	19	37
	Yes	3 (1.5)	2 (1.0)	5 (1.2)
	No	202 (98.5)	205 (99.0)	407 (98.8)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 11. Neonatal Care - Only Alive Births

11.2.1 Neonatal Care

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Care after delivery (n(%))	Missing	1	1	2
	Normal Care	185 (84.5)	196 (92.0)	381 (88.2)
	Special Care	14 (6.4)	7 (3.3)	21 (4.9)
	Level 2 intensive care (ie high dependency intensive care)	9 (4.1)	6 (2.8)	15 (3.5)
	Level 1 intensive care (maximal intensive care)	6 (2.7)	1 (0.5)	7 (1.6)
	Other	5 (2.3)	3 (1.4)	8 (1.9)
Any Congenital Abnormality (n(%))	Missing	3	5	8
	Yes	8 (3.7)	7 (3.3)	15 (3.5)
	No	209 (96.3)	202 (96.7)	411 (96.5)
Other Hospital Admission (n(%))	Missing	16	9	25
	Yes	3 (1.5)	2 (1.0)	5 (1.2)
	No	201 (98.5)	203 (99.0)	404 (98.8)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 11. Neonatal Care - Only Alive Births

11.2.2 Neonatal care after delivery - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of Care_Deliv by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
Care_Deliv	*METFORMIN*	*PLACEBO*	*Total*
Missing	1	1	.
No	199	190	389
Yes	14	29	43
Total	213	219	432

Frequency Missing = 2

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
Care_Deliv_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.461	0.236	0.899	0.0231	0.0242

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*Analised using logistic regression (binary logit), probability modeled is Care_Deliv='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_11_2_Neonatal_unit.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 11. Neonatal Care - Only Alive Births

11.2.3 Any Congenital Abnormality - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of Abnormal by AllocatedTreatment

Abnormal	*AllocatedTreatment(Allocated Treatment) METFORMIN*	*PLACEBO*	*Total*
Missing	5	3	.
No	202	209	411
Yes	7	8	15
Total	209	217	426

Frequency Missing = 8

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
Abnormal_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.905	0.322	2.543	0.8503	1.0000

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*Analised using logistic regression (binary logit), probability modeled is Abnormal='Yes'
#Significance level set at p<0.05
Detailed analysis in file 'Empowar_11_2_Neonatal_unit.lst'

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Section 12. Maternal symptoms up to 36 weeks gestation

12.1.1 Taste Disturbance - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Taste Disturbance (n(%))	Missing	25	27	52
	Yes	32 (16.2)	25 (12.6)	57 (14.4)
	No	166 (83.8)	174 (87.4)	340 (85.6)
Taste Disturbance severity (n)	Mild	19	13	32
	Moderate	12	7	19
	Severe	1	5	6

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Section 12. Maternal symptoms up to 36 weeks gestation

12.1.2 Taste Disturbance - Statistical analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of TasteDis_ana by AllocatedTreatment*

TasteDis_ana(Taste disturbance at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	25	32	57
No	174	166	340
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
tastedis_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.745	0.424	1.311	0.3077	0.3200

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*Analised using logistic regression (binary logit), probability modeled is TasteDis_ana='Yes'

#Significance level set at p<0.05

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Section 12. Maternal symptoms up to 36 weeks gestation

12.2.1 Skin Reaction - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Skin Reaction (n(%))	Missing	25	27	52
	Yes	39 (19.7)	36 (18.1)	75 (18.9)
	No	159 (80.3)	163 (81.9)	322 (81.1)
Skin Reaction severity (n)	Mild	23	22	45
	Moderate	14	11	25
	Severe	2	3	5

Section 12. Maternal symptoms up to 36 weeks gestation

12.2.2 Skin Reaction - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of SkinReac_ana by AllocatedTreatment*

SkinReac_ana(Skin Reaction at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	36	39	75
No	163	159	322
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
skinreac_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.900	0.545	1.489	0.6827	0.7022

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*Analised using logistic regression (binary logit), probability modeled is SkinReac_ana='Yes'

#Significance level set at p<0.05

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Section 12. Maternal symptoms up to 36 weeks gestation

12.3.1 Abdominal Pain - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention----------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Abdominal Pain (n(%))	Missing	25	27	52
	Yes	42 (21.2)	49 (24.6)	91 (22.9)
	No	156 (78.8)	150 (75.4)	306 (77.1)
Abdominal Pain severity (n)	Mild	25	28	53
	Moderate	14	18	32
	Severe	3	3	6

Section 12. Maternal symptoms up to 36 weeks gestation

12.3.2 Abdominal Pain - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of AbdoPain_ana by AllocatedTreatment*

AbdoPain_ana(Abdominal Pain at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	49	42	91
No	150	156	306
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
abdopain_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.213	0.759	1.940	0.4192	0.4740

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*Analised using logistic regression (binary logit), probability modeled is AbdoPain_ana='Yes'

#Significance level set at p<0.05

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Section 12. Maternal symptoms up to 36 weeks gestation

12.4.1 Flatulence - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Flatulence (n(%))	Missing	25	27	52
	Yes	44 (22.2)	51 (25.6)	95 (23.9)
	No	154 (77.8)	148 (74.4)	302 (76.1)
Flatulence severity (n)	Mild	27	19	46
	Moderate	14	23	37
	Severe	3	9	12

Section 12. Maternal symptoms up to 36 weeks gestation

12.4.2 Flatulence - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of Flatu_ana by AllocatedTreatment*

Flatu_ana(Flatulence at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	51	44	95
No	148	154	302
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
flatu_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.206	0.760	1.915	0.4268	0.4806

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*Analised using logistic regression (binary logit), probability modeled is Flatu_ana='Yes'
#Significance level set at p<0.05
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Section 12. Maternal symptoms up to 36 weeks gestation

12.5.1 Constipation - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Constipation (n(%))	Missing	25	27	52
	Yes	57 (28.8)	57 (28.6)	114 (28.7)
	No	141 (71.2)	142 (71.4)	283 (71.3)
Constipation severity (n)	Mild	33	32	65
	Moderate	21	17	38
	Severe	3	8	11

Section 12. Maternal symptoms up to 36 weeks gestation

12.5.2 Constipation - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of Consti_ana by AllocatedTreatment*

Consti_ana(Constipation at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	57	57	114
No	142	141	283
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
consti_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.993	0.643	1.534	0.9746	1.0000

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*Analised using logistic regression (binary logit), probability modeled is Consti_ana='Yes'

#Significance level set at p<0.05

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Section 12. Maternal symptoms up to 36 weeks gestation

12.6.1 Diarrhoea - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Diarrhoea (n(%))	Missing	25	27	52
	Yes	37 (18.7)	83 (41.7)	120 (30.2)
	No	161 (81.3)	116 (58.3)	277 (69.8)
Diarrhoea severity (n)	Mild	21	49	70
	Moderate	14	24	38
	Severe	2	10	12

Section 12. Maternal symptoms up to 36 weeks gestation

12.6.2 Diarrhoea - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of Diarrh_ana by AllocatedTreatment

Diarrh_ana(Diarrhoea at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	83	37	120
No	116	161	277
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
diarrh_itt	AllocatedTreatment METFORMIN vs PLACEBO	3.113	1.975	4.908	<.0001	0.0000

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*Analised using logistic regression (binary logit), probability modeled is Diarrh_ana='Yes'

#Significance level set at p<0.05

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Section 12. Maternal symptoms up to 36 weeks gestation

12.7.1 Nausea - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Nausea (n(%))	Missing	25	27	52
	Yes	79 (39.9)	97 (48.7)	176 (44.3)
	No	119 (60.1)	102 (51.3)	221 (55.7)
Nausea severity (n)	Missing	1	0	1
	Mild	48	50	98
	Moderate	25	38	63
	Severe	5	9	14

Section 12. Maternal symptoms up to 36 weeks gestation

12.7.2 Nausea - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of Nausea_ana by AllocatedTreatment*

Nausea_ana(Nausea at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	97	79	176
No	102	119	221
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
nausea_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.432	0.962	2.132	0.0765	0.0861

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 00:26

By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is Nausea_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

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DOI: 10.3310/eme03070

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Section 12. Maternal symptoms up to 36 weeks gestation

12.8.1 Vomiting - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Vomiting (n(%))	Missing	25	27	52
	Yes	43 (21.7)	63 (31.7)	106 (26.7)
	No	155 (78.3)	136 (68.3)	291 (73.3)
Vomiting severity (n)	Missing	1	0	1
	Mild	25	31	56
	Moderate	13	26	39
	Severe	4	6	10

Section 12. Maternal symptoms up to 36 weeks gestation

12.8.2 Vomiting - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency — *Table of Vomit_ana by AllocatedTreatment*

Vomit_ana(Vomit at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	63	43	106
No	136	155	291
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
vomit_itt	AllocatedTreatment METFORMIN vs PLACEBO	1.670	1.064	2.621	0.0259	0.0309

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*Analised using logistic regression (binary logit), probability modeled is Vomit_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

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Section 12. Maternal symptoms up to 36 weeks gestation

12.9.1 Headache - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Any Headache (n(%))	Missing	25	27	52
	Yes	66 (33.3)	65 (32.7)	131 (33.0)
	No	132 (66.7)	134 (67.3)	266 (67.0)
Headache severity (n)	Mild	37	38	75
	Moderate	19	19	38
	Severe	10	8	18

Section 12. Maternal symptoms up to 36 weeks gestation

12.9.2 Headache - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of Headache_ana by AllocatedTreatment

Headache_ana(Headache at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
	27	25	.
Yes	65	66	131
No	134	132	266
Total	199	198	397

Frequency Missing = 52

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
headache_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.970	0.638	1.474	0.8871	0.9152

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By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is Headache_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

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Section 13. Serious Adverse Events

13.1.1.1 Mothers with at least one SAE

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Number of Patient with a SAE (n)	OVERALL	41	37	78

Section 13. Serious Adverse Events

13.1.1.2 Mothers with at least one SAE - Statistical Analysis - POST-HOC*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Frequency

Table of ANY_SAE by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
ANY_SAE	*METFORMIN*	*PLACEBO*	*Total*
Missing	1	1	.
No	188	181	369
Yes	37	41	78
Total	225	222	447

Frequency Missing = 2

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
pat_sae_itt	AllocatedTreatment METFORMIN vs PLACEBO	0.869	0.533	1.417	0.5731	0.6189

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*Analised using logistic regression (binary logit), probability modeled is ANY_SAE='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_13_1_1_Npatients_SAE_analysis.lst'

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Section 13. Serious Adverse Events

13.1.1.3 SAE related to the mothers

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Number of SAE (n)	OVERALL	47	42	89
Number of SAE by relationship (n)	Possibly	2	3	5
	Unrelated	45	39	84
Number of SAE by expectedness (n)	Yes	11	11	22
	No	34	29	63
	Unk	2	2	4

Section 13. Serious Adverse Events

13.1.1.3 SAE related to the mothers (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of SAE by outcome (n)	Missing	1	0	1
	Completely recovered	43	33	76
	Condition improving	1	3	4
	Condition improving | Completely recovered	1	0	1
	Condition improving | Recovered with sequelae	0	1	1
	Condition still present and unchanged	0	1	1
	Recovered with sequelae	1	4	5

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Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
11136	METFORMIN	19JAN2012	14JAN2012	Diagnosis: Placental abruption. Drescription: Patient presented at 35+2 weeks gestation with a minor ante-partum haemorrage. Clinical diagnosis of placental abruption was made. necessitating immediate delivery by caesarean section. Diagnosis was confirmed at delivery. Mother and baby are both well. Severity: Moderate	Involved or prolonged inpatient hospitalisation| Life-threatening		Unrelated	No	Completely recovered	17JAN2012
11317	METFORMIN	05MAR2012	02MAR2012	Diagnosis: Venous sinus thrombosis Description: Developed headaches at 22 weeks gestation. MRI confirmed bilateral non-occlusive thrombi in the terminal transverse sinuses and the sigmoid sinus. Commenced on treatment with dalterparin. Outpatient management only. did not require admission to hospital. Diagnosis made on 02/03/12. PI only became aware 05/03/12. Follow-up 20/02/14: Venous sinus thrombosis provoked by pregnancy. Treated with 12 months of LMWH. Now completely resolved. Severity: Moderate	Life-threatening		Unrelated	No	Completely recovered	13MAR2013
11501	METFORMIN	14NOV2012	27OCT2012	Diagnosis: Unknown Description: Admitted with severe renal pain and vomiting. Noted to have deranged LFTs. Recent course of amoxicillin from GP for chest infection. Symptoms and LFTs resolved spontaneously. Severity: Mild	Involved or prolonged inpatient hospitalisation		Possibly	Yes	Completely recovered	31OCT2012
11686	METFORMIN	02APR2013	02APR2013	Diagnosis: Breast Cancer. Description: Has been attending the breast clinic for past 10 days. biopsy of a breast lump. Will require chemotherapy. early induction of labour. followed by surgery. radiotherapy aand further chemoherapy. Follow-up 20/02/14: Developed breast cancer in second trimester of pregnancy. Commenced chemotherapy during pregnancy. elective delivery at 35 weeks gestation. completion of chemotherapy following delivery and then proceeded to mastectomy followed by postoperative radiotherapy. Continues to have oncology follow-up. Severity: Severe.	Other significant medical events (as defined in protocol)| Life-threatening		Unrelated	No	Condition improving	.
11748	METFORMIN	12DEC2013	11DEC2013	Diagnosis: Mastitis. Description: Sepsis secondary to Mastitis. Follow-up 20/02/14: Admitted 10 days postnatal with mastitis. Treated with IV then oral antibiotics. Severity: Moderate	Involved or prolonged inpatient hospitalisation	UTI. 25/09/2013 - 27/09/2013. medication required.	Unrelated	No	Completely recovered	14DEC2013
11748	METFORMIN	27SEP2013	25SEP2013	Diagnosis: Pain and Vomiting. Description: Self presented with upper abdominal pain and vomiting. ?UTI. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Depression from 2009 to 2010. Urinary Tract Infection. April 5th 2013 to 6.4.2013.	Unrelated	No	Recovered with sequelae	27SEP2013
11748	METFORMIN	07OCT2013	06OCT2013	Diagnosis: Abdominal Pain ? Preterm Labour Description: Self presented with abdo pain. ?Preterm labour complicated by urinary tract infections. Severity: Moderate Follow-up 20/02/14: Diagnosis: UTI. Admitted at 32 weeks gestation with abdominal pain. Urine culture +ve for e.coli. Threatened pre-term labour excluded. Treated with antibiotics and resolved. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Urinary Tract Infection. 02/04/13 - 05/04/2013 and 25/09/2013 - 26/09/2013. medication required for both infections.	Unrelated	No	Completely recovered	09OCT2014
11797	METFORMIN	18NOV2013	14NOV2013	Diagnosis: Vomiting in late pregnancy. Description: Self presented with excessive vomiting. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Hyperemesis. 20/05/13. ongoing. medication required.	Possibly	Yes	Completely recovered	15NOV2013
11880	METFORMIN	28NOV2013	28NOV2013	Diagnosis: Intrauterine Death. Description: Patient attended for ultrasound scan for fetal anomaly at 20+1 weeks gestation. No fetal heartbeat seen. IUD performed. Follow-up 20/02/14: Diagnosis: Midtrimester fetal loss. Fetal death diagnosed on routine anomaly scan at 20+ weeks. Admitted for medical management of miscarriage on 30/11/2013. Home on 1/12/2013. Severity: Severe.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	01DEC2013
11881	METFORMIN	07JAN2014	30DEC2013	Diagnosis: Severe Sepsis. Description: Admitted at 30+4 weeks gestation with pyrexia. rigors and dysuria. Treated with multiple antibiotics for presumed urosepsis. Clinical deterioration over the course of a week. Decision made to deliver baby in maternal interest at 31+2 weeks gestation. Patient transferred to ITU for ventilatory support post delivery. Continues to improve. back in normal ward at present. Follow-up 14/01/14: Diagnosis: Probable urosepsis and atypical pneumonia necessitating preterm delivery in maternal interest. Description: Condition now resolved. patient recovered. Severity: Severe.	Life-threatening| Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	13JAN2014

Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
11884	METFORMIN	03FEB2014	17DEC2013	Diagnosis: Probable preterm labour spontaneous rupture of membranes. Description: Initially presented at 21+ weeks gestation with vague history of possible SRM. Admitted to hospital for overnight observation and then reviewed weekly at DAU at St Johns Hospital Livingston. Diagnosis of SRM more probable at 23 weeks. Treated with 10 days erythromycin and prophylactic steroids at 24 weeks. Continues to be seen thrice weekly as an outpatient at St Johns. Patient did not inform research team. Did not attend for scheduled study visit today. which is when this came to our attention. Had discontinued study medication around 20 weeks gestation due to side effects. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Condition still present and unchanged	.
12008	METFORMIN	13FEB2012	09FEB2012	Atonic uterus resulting in massive obstetric haemorrage. 2 litre loss. Severity: Severe	Life-threatening	N/a	Unrelated	No	Completely recovered	12FEB2012
12008	METFORMIN	16AUG2012	14FEB2012	Diagnosis: Chest Pain Description: Chest pain following LSCS 5/7 days after delivery. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	16FEB2012
12041	METFORMIN	07NOV2012	07NOV2012	Diagnosis: Termination of pregnancy (TOP) Description: TOP due to confirmed Down's Syndrome by amniocentesis. Severity: severe	Involved or prolonged inpatient hospitalisation	No relevant medical history	Unrelated	No	Completely recovered	10NOV2012
12056	METFORMIN	16APR2013	30MAR2013	Diagnosis: Fetal Supraventricular Tachycardia Description: Patient attended on LW with a history of reduced fmf. CTL detected FHR of 200bpm. USS diagnosis fetal supraventricular tachycardia. Patient admitted and medicated wih flecainide 100mg TDS. Follow-up 30/05/13: Diagnosis: Admitted with reduced fmf. Description: Admitted to antenatal ward with reduced fetal movements. On USS baby found to have cardiac abnormalities - SVT and hydrops. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Recovered with sequelae	05APR2013
12060	METFORMIN	16SEP2013	03SEP2013	Diagnosis: Postpartum Haemorrhage. Description: Kiwi delivery of male infant. PPH following delivery of 1.6 litres. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	05SEP2013
12076	METFORMIN	07NOV2013	04NOV2013	Diagnosis: ?Admitted DVT. Description: Client c/o groin and leg pain. ? DVT. Admitted to antenatal ward overnight. Dopplers normal. Follow-up 19/11/2013: Diagnosis: Right sided groin pain. Description: Complained of right sided groin pain and vulval swelling. Consultant review - admitted to ward for observation for ? pelvis thrombosis. XXX and anti-embotic treatment. Doppler of right leg 05/11/13 - no evidence of deep vein thrombosis. Discharged home 05/11/13. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	18NOV2013
12079	METFORMIN	20JAN2014	08DEC2013	Diagnosis: Suspected Urinary Tract Infection. Description: Self referred to labour ward triage with abdominal pain. back pain. diarrhoea (once only) and reduced fetal movements for one week. Antibiotics given for suspected urinary tract infection. Not admitted - discharged home after 2hrs 10 minutes. Severity: Mild	Other significant medical events (as defined in protocol)		Unrelated	No	Completely recovered	23DEC2013
12093	METFORMIN	03APR2014	30MAR2014	Diagnosis: Postpartum Haemorrhage. Description: Postpartum haemorrhage of 1500mls following IOL. prolonged labour and vaginal delivery. Postpartum syntocinon commenced. catheterised. Hb 100g/ld. Discharged home 01/04/2014. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	01APR2014
12096	METFORMIN	06MAR2014	13FEB2014	Diagnosis: ? Preterm labour/Reduced Fetal Movements. Description: Admitted to antenatal ward with tightenings - speculum os closed. Reduced fetal movements for 1 week. Admitted for overnight observation. Tightenings settled. Discharged home 14/2/14 with routine follow-up in antenatal clinic. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	14FEB2014
12099	METFORMIN	31DEC2013	30DEC2013	Diagnosis: Suspicion of pre-eclampsia. Description: Admitted with headaches. high blood pressure and proteinuria at 25+1. Remains an inpatient for observation. Not on any medication. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	03JAN2014
13082	METFORMIN	07FEB2012	04FEB2012	Admitted for labile BP at 39 weeks. Commenced on labetalol 100mgs BD and IOL booked. Inpatient on Mat ward since 04/02/12. Completion of data 09/05/13: Participant delivered on 08.2.12 and was discharged on 11.2.12. On review of medical notes. hypertension resolved postnatally; was not discharged on any anti-hypertensives. Severity: Mild	Involved or prolonged inpatient hospitalisation	Has history of hypertension. was on Irbesartan 75mgs daily in 2009. Not on treatment since	Unrelated	Yes	Completely recovered	11FEB2012
13147	METFORMIN	04MAY2012	28FEB2012	Diagnosis: Recurrant PV bleeds from cervical erosion Description: Has had recurrant PV bleeds of varying amounts throughout pregnancy. Diagnosed as cervical erosion. Not admitted at any stage. IOL booked at term due to this history. Severity: Moderate	Other significant medical events (as defined in protocol)		Unrelated	Yes	Completely recovered	15MAY2012
13209	METFORMIN	31AUG2012	24AUG2012	Diagnosis: Inpatient stay for over 24hrs for investigations. All negative. Description: Reported chest pain and calf pain at day 4 postnatal. Admited to hospital for 2 days for chest x-ray and blood tests to rule out PE. Was commenced on Fragmin for 6/52 and attended for leg Doppler x 2. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	04SEP2012

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Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
13248	METFORMIN	24APR2012	22MAR2012	Diagnosis: Abdominal Pain due to IBS Description: Admitted to emergency room at 17/40 with abo pain 22.03/12. ? Renal cholic. admitted to ward and investigated. Treated with IV antiemetics as vomitting. USS normal. Discharged 24/03/12 with oral antiemetics. Discharge diagnosis IBS. Participant reported diahorrea and abdominal cramps for several days before attending hospital. whilst on study medication. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Possibly	Yes	Completely recovered	24MAR2012
13528	METFORMIN	19MAR2013	12MAR2013	Diagnosis: ?DVT. Description: Patient admitted to antenatal ward on 12.3.13 with shortness of breath and chest pain ??DVT. Had all appropriate investigations including chest xray. leg Doppler and ECG. All investigations normal. Received fragmin 10.000iu BD until diagnosis. Discharged home the following day to normal care. for follow up in consultant clinic 22.3.13. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	Unk	Recovered with sequelae	19MAR2013
13551	METFORMIN	05MAR2013	02MAR2013	Diagnosis: Emcs for fetal distress. followed by 5000ml PPH and hysterectomy. Description: Background: NI has been having close monitoring in pregnancy for raised BP. She was commenced on labetalol on 2.1.13. Had subsequent admission for raised BP 6.2.13 (not an SAE according to protocol). Discharged back to community care the following day. Admitted to antenatal ward again with raised BP on 25.2.13. Remained an inpatient until IOL commenced 28.2.13 at 20.30 at 38 weeks gestation. Baby: EMCS for fetal distress (CTG and FBS) under GA. Baby delivered at 1913. apgars 4 at 1 minute. 9 at 10 minutes. Cord Ph's 7.18. 7.24. Baby was admitted to NICU overnight due to NI being transferred to Whiston. Re-united with mum when returned to Liverpool Women's. NI: Following emcs NI suffered from major haemorrhage totalling 5000ml. A hysterectomy was undertaken. NI received a total of 7 units of blood (including 500ml cell salvaged blood) and 1 unit of FFP. She also had a dextrose infusion to correct transfusion-related hypo	Involved or prolonged inpatient hospitalisation| Life-threatening	Raised BP. start 2.1.13. ongoing. medication required.	Unrelated	Yes	Condition improving | Recovered with sequelae	07MAR2013
13553	METFORMIN	23JAN2013	21JAN2013	Diagnosis: Admitted for raised BP and proteinuria. Description: MR was admitted to the antenatal ward on 21/01/13 for raised BP and proteinuria at 26+3/40. She has been commenced on labetalol 200mg BD and is staying in for observation presently. F/up 25/01/13. Her BP dropped and the labetalol dose was reduced to 100mg BD. She was discharged home on 24.1.13 with an appointment at the day ward for a BP profile and CTG on Monday 28.1.13 with the plan to stop labetalol if BP normal. Severity: Mild	Involved or prolonged inpatient hospitalisation	Pregnancy induced hypertension with significant proteinuria. start 2008. not ongoing. medication required. Pregnancy induced hypertension. start 2010. not ongoing. medication required.	Unrelated	Yes	Completely recovered	24JAN2013
14035	METFORMIN	28NOV2011	26NOV2011	Had upper right quadrant pain since approx 28 weeks. Admitted to hospital on 26/11/2011 and discharged home on the 27/11/2011. No cause for this has been found. LFT's raised and pain now increasing admitted to hospital again today for urgent induction of labour planned. Her hospital consultant has recommended that the study drugs should be stopped.	Involved or prolonged inpatient hospitalisation	N/A	Unrelated	No	Recovered with sequelae	06DEC2011
14161	METFORMIN	24DEC2012	24DEC2012	Neville Barnes Forceps delivery on 24/12/2012 at 01.17am. Postpartum haemorrhage of 1500ml. thought to be in part due to a spurting blood vessel from episiotomy wound and vaginal tears. Transferred to high dependency unit. Hb 7.7g/dl at 07.16am. Patient offered blood transfusion. she is unsure at time of reporting SAE whether she wishes to accept this. Participant withdrew from the EMPOWaR study on 11/11/2012 at her request. She was taking one study tablet per day up until that date.	Involved or prolonged inpatient hospitalisation	N/A	Unrelated	No	Completely recovered	25DEC2012
14162	METFORMIN	12DEC2012	11DEC2012	Emergency L.S.C.S for failure to progress in labour. Post Partum Haemorrhage of 1200mls	Involved or prolonged inpatient hospitalisation	N/A	Unrelated	No	Completely recovered	14DEC2012
14303	METFORMIN	08AUG2013	08AUG2013	Post Partum Haemorrhage 1200mls.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	08AUG2013
16029	METFORMIN	09MAY2013	03SEP2012	Abdo pain and reduced fetal movements. Description: Abdo pain - intermittent - and reduced fetal movements. Admitted for observation. Contraction type pains 1:20 mins. Settled. Discharged 05/09/2012. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	05SEP2012
16121	METFORMIN	24JUN2013	30MAY2013	Diagnosis: Pyelonephritis Description: Pyelonephritis - ascending UTI involving pyelum. fever. tachycardia. abdo/back pain. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	04JUN2013
21089	METFORMIN	28MAR2014	17JAN2014	Diagnosis: Hyperemesis. Description: Admitted to maternity ward overnight with hyperemesis. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Removal of brain hernia (Arnold-Chiari malformation). 18/01/2013.	Unrelated	No	Completely recovered	18JAN2014

Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
24010	METFORMIN	28SEP2013	16SEP2013	Diagnosis: Emergency Caesarean Section Post Partum Haemorrhage 1500mls. Description: Caesarean section for fetal distress at T+15 during induction of labour. Estimated blood loss at caesarean section 1500mls. Baby's birth weight 3888 - all normal. Severity: Moderate	Involved or prolonged inpatient hospitalisation	PCOS. ongoing. medication not required.	Unrelated	Unk	Completely recovered	18SEP2013
25180	METFORMIN	25JUN2013	14JUN2013	Diagnosis: Pain and ?Pyelonephritis. ?Cholelithiasis. Description: Admitted 14/06/13 overnight to Chesterfield Royal Hospital with dysuria. back pain. feeling unwell. Intravenous antibiotics overnight. discharged 15/06/13 on oral antibiotics. admitted Scunthorpe Hospital 17/06/13 overnight with severe right upper abdominal pain. Antibiotics changed. Ultrasound scan diagnosed cholelithiasis. Discharged 18/06/13 home with antibiotics and advice to see surgical review post pregnancy and low fat diet. Severity: Moderate	Involved or prolonged inpatient hospitalisation	Asthma. ongoing. medication required.	Unrelated	No	Condition improving	.
25232	METFORMIN	17OCT2013	14OCT2013	Diagnosis: Preterm Labour Spontaneous Rupture of Membranes. Description: Spontaneous rupture of membranes occurred 14/10/2013 at 13.30. No uterine activity. On 15/10/2013 developed maternal tachycardia and increase of white blood cells. Decision made at 10:50 on 15/10/13 to induce labour. Labour augmented with syntocinon infusion. Live baby girl born on 16/10/2013 at 07.14hrs. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	16OCT2013
25264	METFORMIN	15AUG2013	08AUG2013	Diagnosis: benign Intracranial Hypertension. Description: Admitted to Hallamshire Hospital with headache due to this. Had lumbar puncture to drain some CSF. Symptoms resolved. had one night in hospital. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Benign Intracranial Hypertension. started in 2009. ongoing. medication not required.	Unrelated	No	Completely recovered	09AUG2013
25264	METFORMIN	01OCT2013	26SEP2013	Diagnosis: Raised intra-cranial pressure. Description: Admission to Chesterfield Royal Hospital with headache. blurred vision. tinnitus. nausea 26/09/13. Lumbar puncture eased symptoms but backache marked after procedure and thought to be related to same. Care continued with analgesic therapy and physio. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Idiopathic Intracranial Hypertension. start spring 2009. end late 2011. and received medication between these dates. Diagnosed in 2009. ongoing and no medication required as contra-indicated in pregnancy.	Unrelated	Yes	Condition improving	.
25459	METFORMIN	11APR2014	06APR2014	Diagnosis: Left Calf Pain ?Thrombosis. Description: Admitted with unilateral calf pain. No redness or swelling. x1 dose anti-coagulant and analgesia given. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	07APR2014
25459	METFORMIN	17JUN2014	16JUN2014	Diagnosis: Right ovarian cyst Admitted to birth centre with right sided abdominal pain on 16.06.14. C/section performed 17.06.14. Severity: Mild	Involved or prolonged inpatient hospitalisation	Right adnexal cyst (15/03/14)	Unrelated	No	Completely recovered	17JUN2014
11263	PLACEBO	29MAY2012	27MAY2012	Diagnosis: Post partum haemorrhage Description: Required delivery by caesarian section for failure to progress into labour. Had atonic post partum haemorrhage of 2000mls requiring examination under anaesthetic and use of Bakri balloon. Severity: Moderate	Life-threatening| Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	30MAY2012
11323	PLACEBO	29MAY2012	20MAY2012	Diagnosis: Inconclusive Description: Admitted with shortness of breath and chest pain at 32 weeks gestation. Investigated thoroughly with CTPA. upperabdo ultrasound and blood tests but all investigation negative. Symptoms settled spontaneously. Severity: Moderate	Involved or prolonged inpatient hospitalisation	Asthma. ongoing. medication required Smoker. ongoing	Unrelated	No	Completely recovered	22MAY2012
11335	PLACEBO	21JUN2012	19JUN2012	Diagnosis: Post partum haemorrhage Description: Delivered by elective caesarian section on 19/06/12. Developed bleeding secondary to uterine atony following delivery while in recovery area. Rushed to theatre for EUA under GA. Haemorrhage managed with Bakri balloon. Estimated blood loss 2000mls. Severity: Moderate	Involved or prolonged inpatient hospitalisation| Life-threatening		Unrelated	No	Completely recovered	21JUN2012
11643	PLACEBO	20MAR2013	13MAR2013	Diagnosis: Abdominal Pain. Description: Admitted with abdominal pain. originally though to be ligamentous. Developed diarrhoea and vomiting Saturday 16/03/13. Stool sample result on 19/03/13 - c.diff. 20/03/13 well. no D + V since 18/3/13. commenced metronidazole. For discharge home today. Severity: Severe Follow-up 20/02/2014: Diagnosis: Clostridium Difficile Diarrhoea. Admitted with abdominal pain. Developed diarrhoea and vomiting during admission. Stool culture +ve for C.diff. Treated with IV fluids and oral metronidazole. Discharged home on 20/03/2013. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	20MAR2013

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DOI: 10.3310/eme03070

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Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
11714	PLACEBO	30SEP2013	27SEP2013	Diagnosis: Large Blood Loss - 1500ml. Description: Emergency c/s for failure to progress in labour. 1500ml blood loss at delivery. Follow-up 20/02/14: Diagnosis: Post Partum Haemorrhage. Atonic postpartum haemorrhage following emergency caesarean section for failure to progress in the 1st stage of labour. Estimated blood loss 1500ml. Severity: Moderate.	Life-threatening| Involved or prolonged inpatient hospitalisation	Gestational Diabetes Mellitis. 09/07/13. ongoing. no medication required.	Unrelated	No	Completely recovered	03OCT2013
11786	PLACEBO	07OCT2013	04OCT2013	Diagnosis: Pre-term rupture of membranes. Description: Spontaneous pre-term. pre-labour rupture of membranes. Severity: Severe Follow-up 20/02/14: Diagnosis: Spontaneous preterm rupture of membranes. Preterm SRM at 25+ weeks gestation. Managed as an outpatient until 28+ weeks when developed blood stained liquor. Admitted to hospital on 24/10/13. Managed conservatively as an inpatient until 4/11/13 when went into labour. Baby delivered on 4/11/13. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Nil of note.	Unrelated	No	Completely recovered	04NOV2013
11940	PLACEBO	04JUN2014	02JUN2014	Diagnosis: Respiratory Tract Infection. Presented with cough and feeling generally unwell at 37+ weeks gestation. Already taking amoxicillin and prednisolone prescribed by GP. Also complaining of reduced fetal movements. Admitted to hospital for optimisation of treatment and observation. Chest xray normal. Reviewed by respiratory physician and symptoms felt to be improving. likely viral origin. no further antibiotics or prednisolone required. advised to monitor PEFR and for GP to refer to outpatient respiratory clinic as necessary. Following Obstetric review. in view of persistently reduced fetal movements and recent diagnosis of gestational diabetes decision made for induction of labour. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	04JUN2014
12010	PLACEBO	28MAR2012	09MAR2012	Post partum haemorrhage - 500mls. At emergency section	Other significant medical events (as defined in protocol)		Unrelated	Yes	Completely recovered	11MAR2012
12013	PLACEBO	26MAR2012	26MAR2012	Post partum haemorrhage - 600ml following emergency section	Other significant medical events (as defined in protocol)		Unrelated	Yes	Completely recovered	26MAR2012
12043	PLACEBO	11MAR2013	07MAR2013	Diagnosis: Abdominal Pain Description: Client admitted at 35+6/40 with abdominal pain - ?UTI. ?Preterm labour ?D+V. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	09MAR2013
12059	PLACEBO	25JUL2013	27JUN2013	Diagnosis: EMCS. Description: EMCS at 33/40 for reduced fmf. reduced AFI. No EDF. Severity:	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	28JUN2013
12074	PLACEBO	04NOV2013	12OCT2013	Diagnosis: Small bleed per vaginum. Description: Patient self referred to labour ward triage with small bleed per vaginum and mild abdominal pain/ Speculum performed. cervical OS closed. Scan - no problems seen. Admitted to antenatal ward overnight for observation. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	13OCT2013
12077	PLACEBO	14NOV2013	13NOV2013	Diagnosis: Pre-term labour. Description: Preterm spontaneous vaginal delivery at 34+6 weeks of female infant. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	15NOV2013
12086	PLACEBO	02OCT2013	08SEP2013	Diagnosis: SROM @ 18+4 Medical TOP. Description: Medical termination of pregnancy due to SROM. Spontaneous vaginal delivery of foetus. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	12SEP2013
12091	PLACEBO	26MAR2014	23MAR2014	Diagnosis: Baby admitted to SCBU with meconium aspirate. Description: Patient had emergency c/s for fetal distress. Baby had poor apgar and was admitted to SCBU - CTU. Ventilated. Baby improving and extabated 25/3/2014. Mum discharged home 26/05/14. Severity: Severe. Follow-up 19/05/14: Baby ventilated after delivery - poor apgars. Baby discharged home 06/04/14. No follow-up. Mum contacted baby doing well - no concerns.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	16MAY2014
12104	PLACEBO	13MAR2014	11MAR2014	Diagnosis: ?UTI. Description: Admitted to triage via GP with history of pelvic pain. vomiting and feeling unwell. Pyrexia on admission. Admitted to antenatal ward for intravenous antibiotics and antiemetics. IV fluids. Discharged home with oral antibiotics 13/3/14. Apyrexial since admission. Severity:	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	13MAR2014
13007	PLACEBO	05AUG2011	28JUL2011	Diagnosis: prolonged hospital stay. Participant induced for suspected IUGR at 40 weeks+1day. Baby's BW below 9th centile. therefore needed blood sugar recordings (TBGs) pre and post feeds as per protocol. Baby BW 2.72kgs. These were completed within 24hrs. This resulted in a prolongation of hospital stay. 12/08/2011 IUGR is an Expected outcome and is being routinely collected as a secondary outcome of this study. Therefore. not a SUSAR but a SAR.	Involved or prolonged inpatient hospitalisation	2008 - normal vaginal delivery at term (41 weeks). 3100gms	Possibly	Yes	Completely recovered	28JUL2011
13144	PLACEBO	11MAY2012	31MAR2012	Diagnosis: Symphysis Pubis Pain. Physiological Faints in Pregnancy Description: Occasional fainting episodes and episodes of raised BP over past 6 weeks. 48hrs admission on ward for observation due to this. Also reports SPD. IOL at 36+7 booked for this reason. However on admission to IOL suite was found to be 36+6. reasons for IOL did not warrant delivery at this gestation. had been incorrectly calculated when IOL booked. therefore IOL rebooked and performed at 38+1 on 22/05/12. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	22MAY2012

Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
13301	PLACEBO	19OCT2012	17OCT2012	Diagnosis: Intrapartum and postpartum haemorrhage of 2000mls Description: This lady was iduced at 41+5 for postdates pregnancy. She received 2mg x 2 of Prostin gel. Prior to ARM she had fresh bleeding PV. Oblique breech lie was diagnosed on USS. She was taken to theatre for emergency caesarean section. Intrapartum haemorrhage = 1000ml. postnatal haemorrhage = 1000ml. Total EBL = 2000ml. Baby born with Apgars 10 at 1 minute and 10 at 5 minutes. Cord ph's 7.26 and 7.28. Baby's weight = 4440g. AF well on demand. The lady was transfused 2 units of blood in theatre. Condition currently improving. today Hb 7.8g/dl. for further 2 units of blood. Follow-up 24/10/12: This lady was discharged home with baby from the postnatal ward on Sunday 20.10.12 at 14.00. Her HB was 8.7g/dl and she was prescribed ferrous sulphate 200mg TDS. Severity: Severe	Involved or prolonged inpatient hospitalisation| Life-threatening	Previous PPH and subsequent blood transfusion in 2007. medication required. PCOS. ongoing. no medication required.	Unrelated	Unk	Completely recovered	20OCT2012
13473	PLACEBO	04JAN2013	03JAN2013	Diagnosis: Neonatal BM's low. Baby admitted to NICU. lowest BM 1.7mmol Description: EP was delivered via emergency c/s. IOL at 36+3 for pre-eclampsia on 3.1.13. Baby was transferred to the neonatal unit for 24 hours post delivery for low BM's. Lowest BM 1.7mmol. baby tube fed only. no IV fluids required. Baby maintaining BM's and back on postnatal ward with mum after 24 hours. Discharged home 5.1.13. no follow-up anticipated. Severity: Mild	Involved or prolonged inpatient hospitalisation		Possibly	Yes	Completely recovered	04JAN2013
13591	PLACEBO	07MAY2013	30APR2013	Diagnosis: Hospital admission via ambulance with gall stones. Description: RB was admitted to Royal Liverpool Hospital on 30.04.13 via ambulance with chronic back pain. She is 3 weeks postnatal. Was kept nil by mouth for 24 hours and had a USS which diagnosed gall stones. Received antibiotics and analgesia whilst an inpatient and was discharged on 01.05.13. RB reports awaiting blood tests to see if presence of infection and has an appointment with a consultant at the Royal on 16.04.13. NB. Information obtained verbally from the patient only. no access to medical notes as attended a different hospital. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	01MAY2013
13705	PLACEBO	02AUG2013	19JUL2013	Diagnosis: APH 31+2/40. Description: Patient admitted to antenatal ward with APH at 31+2/40. Had x 2 small PV bleeds at home. HVS sent. Speculum NAD. Discharged home after 24 hours as nil further PV bleeding. Taking ferrous sulphate. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	20JUL2013
13712	PLACEBO	02AUG2013	23JUL2013	Diagnosis: Obstetric Cholecostasis. Description: Patient presented at 31+5/40 with localised itching. Bile acids taken and indicate obstetric cholecostasis. Patient prescribed Ursodeoxycholic acid 300mg TDS and Chlorphenamine 4mg. IOL booked for 05.09.2013. Having weekly bloods and CTG's. Information obtained from patient via telephone only. Severity: Moderate.	Other significant medical events (as defined in protocol)	Obstetric cholecostasis in previous pregnancy in 2010. Start 27/01/2010. end 02/02/2010. medication required.	Unrelated	Yes	Completely recovered	06SEP2013
13914	PLACEBO	22JAN2014	15JAN2014	Diagnosis: Threatened Preterm Labour. Moderate rise in BP. Description: Threatened Preterm Labour. Admission to consultant unit following abdominal pains. Fibrinectin test positive. Steroids given to cover for potential preterm birth. BP moderately elevated whist an inpatient. Discharged after approx. 48hrs and monitored on community. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	17JAN2014
14036	PLACEBO	23NOV2011	22NOV2011	Post-partum haemorrhage 1000mls - maternal collapse transfered to high dependency unit.	Involved or prolonged inpatient hospitalisation| Other significant medical events (as defined in protocol)	N/A	Unrelated	No	Completely recovered	23NOV2011
14272	PLACEBO	29MAY2013	18APR2013	Sudden onset very severe headache 18.04.13. Admitted to neurological ward for treatment and lumbar puncture. 24 hour stay. Re-admitted 22.04.13 with re-occurrence of headache - diagnosis - this headache related to lumbar puncture. Resolved after 24 hours and discharged. No further headaches.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	23APR2013
14336	PLACEBO	27NOV2013	26NOV2013	Diagnosis: Post partum haemorrhage and pre-eclampsia. Description: Admitted to High Dependency Unit from theatre recovery after total PPH 700mls (at delivery 400mls) requiring prolonged IV syntocinon treatment. In addition had raised BP requiring medication after admission to HDU. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Gestational Diabetes. started 07/11/2013. ongoing. no medication required.	Unrelated	No	Recovered with sequelae	29NOV2013
14336	PLACEBO	23OCT2013	17SEP2013	Diagnosis: Abdominal pain cause unknown. Description: Admitted with abdominal pain for observation. Cause unknown. Possible UTI. Possible 'uterine stretching pain'. Routine blood and urine tests performed. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	23SEP2013
14336	PLACEBO	27NOV2013	20NOV2013	Diagnosis: Infective diarrhoea and vomiting. Description: Prolonged episode of diarrhoea and vomiting causing dehydration. IV fluid rehydration required on admission to hospital on 23/11/2013. Admitted for 24 hours. Had one stat dose labetalol for raised BP whilst an inpatient. Stopped study medication. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Gestational diabetes. started 07/11/2013. ongoing. no medication required.	Unrelated	No	Completely recovered	24NOV2013

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Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
14354	PLACEBO	20DEC2013	17DEC2013	Diagnosis: Threatened pre term labour. Description: G5 P2 33 weeks. admitted with PV bleed and irregular tightenings 17.12.13. Prescribed betamethasone and dalteparin. Hospitalised for observation. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Condition improving | Completely recovered	20JAN2014
15031	PLACEBO	27NOV2013	29OCT2013	Diagnosis: Delivery. Description: Postpartum haemorrhage 1400mls. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	30NOV2013
15034	PLACEBO	07NOV2013	24OCT2013	PPH 1600mls. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	25OCT2013
16052	PLACEBO	08JAN2013	27DEC2012	PPH 1800mls Severity: Moderate	Life-threatening		Unrelated	No	Completely recovered	31DEC2012
17036	PLACEBO	12MAR2013	10MAR2013	Diagnosis: Influenza. Description: Inpatient hospitalisation due to influenza. Patient admitted on 10/03/13. Self discharged on 11/03/13 as feeling better. Study medication stopped whilst unwell. to recommence when well. Severity: Moderate. Follow-up 17/06/2014: Diagnosis: Influenza - resulting in raised ALTs requiring scan. Initial SAE reported due to hospitalisation due to influenza. Following this raised ALT levels were noted and a liver scan arranged. This showed an enlarged spleen ?consistent with recent influenza. This patient has had raised ALT levels dating back to 2010. Discharged home following scan.	Involved or prolonged inpatient hospitalisation| Other significant medical events (as defined in protocol)	Cholecystectomy. 2010 - 30/07/2010.	Unrelated	No	Completely recovered	17JUN2014
17137	PLACEBO	27DEC2013	25DEC2013	Diagnosis: Costochondritis. Description: Admitted with upper abdominal pain - bloods and USS all NAD. Presumed costochondritis. Discharged home 27/12/13. Severity:	Involved or prolonged inpatient hospitalisation	Previous episode of costochondritis	Unrelated	No	Completely recovered	27DEC2013
17137	PLACEBO	20JAN2014	17JAN2014	Admitted to antenatal ward with unstable lie. To remain inpatient until LSCS 24.1.14.	Involved or prolonged inpatient hospitalisation	Episode of costa chondritis	Unrelated	No	Completely recovered	21FEB2014
21033	PLACEBO	23MAY2014	27APR2014	Diagnosis: Abdominal Pain. Likely Costochondritis. Description: Admitted at 33+4 weeks gestation with abdominal pain. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	29APR2014
21033	PLACEBO	23MAY2014	11APR2014	Diagnosis: Likely Costochondritis. Description: Admitted at 31+2 weeks gestation for observation/monitoring for left sided chest pain. Investigations generally NAD. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Condition improving	.
21033	PLACEBO	02APR2014	28DEC2013	Diagnosis: Non-specific chest pain. Description: Admitted via ambulance with suspected clinical suspicion of a pulmonary embolism. Had left pleuritic chest pain. with shortness of breath and collapse. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Caesarean Section. 03/12/2013.	Unrelated	No	Completely recovered	30DEC2013
21069	PLACEBO	19MAR2014	18FEB2014	Diagnosis: Sepsis. Description: Pyrexial and tachycardic in labour. Raised CRP and white cell count. also platelets reduced. Had IV antibiotics. then oral. Went on septic pathway. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	25FEB2014
21093	PLACEBO	23DEC2013	28NOV2013	Diagnosis: Small antepartum haemorrhage. Description: Admitted to maternity ward overnight for observation as PV bleed. Ectropion noted on cervix. Placenta not low-lying. No pain. 23 weeks gestation. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	29NOV2013
21100	PLACEBO	22APR2014	16APR2014	Diagnosis: Antepartum and Postpartum Haemorrhage. Description: Admitted via ambulance in advanced labour. Spontaneous rupture of membranes. then APH of 1200mls. Fetal bradycardia. so forceps delivery. Then required MROP and had PPH of 800mls. Total EBL: 2000mls. Returned to delivery suite for close monitoring and had 2 units of blood transfused. Severity: Severe.	Other significant medical events (as defined in protocol)		Unrelated	No	Completely recovered	18APR2014
21109	PLACEBO	09APR2014	03APR2014	Diagnosis: Small APH - nil on examination. Description: Admitted to maternity ward via maternity day unit with lower abdo discomfort/Braxton hicks/red pv loss/unstable lie. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Gestational Diabetes. 19/03/2014 - 08/04/2014.	Unrelated	No	Completely recovered	05APR2014
21109	PLACEBO	19MAR2014	14FEB2014	Diagnosis: Urinary Tract Infection. Description: Symptomatic of UTI and leukocytes in urine. Admitted for treatment and observation to maternity ward for over 12 hours. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	21FEB2014
25165	PLACEBO	07AUG2013	06AUG2013	Diagnosis: Post Partum Haemorrhage. Description: Following an instrumental vaginal delivery of live male infant, participant had a 2.5 litre blood loss per vagina. Oxytocin administered and hematabate. Blood loss stopped. HB dropped from 103g/L to 76.0g/L and 2 units of blood administered. Participant stable and improving. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	Unk	Completely recovered	07AUG2013

Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*SAE - date of report*	*SAE - date of event*	*Description of SAE*	*Expedited Reporting Criteria*	*Relevant History*	*SAE_related_coded*	*SAE_expected_coded (Y/N)*	*SAE_outcome_coded*	*SAE - date of recovery*
25391	PLACEBO	12MAR2014	07MAR2014	Diagnosis: 1). Musculoskeletal Pain. 2). Depression. Description: Admitted to hospital for observation and analgesia for musculoskeletal pain and depression. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Depression/ Anxiety. started 2005. ongoing. medication required.	Unrelated	No	Missing	.
53072	PLACEBO	30JUN2014	27JUN2014	Diagnosis: Episode of fitting. unknown cause. Description: Singular episode of fitting 5 days postnatal. unknown cause. Admitted to hospital via ambulance. MRI. CT. Chest X ray and blood tests carried out. No abnormality found. declined inpatient stay overnight for observation and had same day discharge. For follow up at 'first fit' clinic. Severity: moderate. UPDATE (01 Oct 2014): Diagnosis: Further reported 4-5 episodes of left sided numbness and tingling on upper body and face. Description: Reported 4 or 5 acute episodes of tingling commencing in left hand and ascending left side of body to face resulting in a heaviness and numb sensation. All occurred within 3 weeks of P/N fit episode and lasted around 5 minutes in duration. Nil since. Has had further ECG at neurology clinic which was normal. Still awaiting results of EEG and MRI.	Involved or prolonged inpatient hospitalisation| Other significant medical events (as defined in protocol)		Unrelated	No	Completely recovered	27JUN2014

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Section 13. Serious Adverse Events

13.2.1 SAE related to the babies

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=223*	*Metformin N=226*	*Overall N=449*
Number of Patient with a SAE (n)	OVERALL	21	14	35
Number of SAE (n)	OVERALL	21	15	36
Number of SAE by relationship (n)	Possibly	1	4	5
	Unrelated	20	11	31
Number of SAE by expectedness (n)	Yes	1	3	4
	No	20	12	32

Section 13. Serious Adverse Events

13.2.1 SAE related to the babies (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of SAE by outcome (n)	Missing	0	1	1
	Completely recovered	12	5	17
	Condition still present and unchanged	5	4	9
	Condition still present and unchanged| Death	0	1	1
	Death	3	2	5
	Recovered with sequelae	1	2	3

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Section 13. Serious Adverse Events

13.2.2 SAE related to the babies - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
11078	METFORMIN	22JUL2011	22JUL2011	Probable congenital cystic adenomatous malformation (CCAM) of fetal lung detected at routine fetal anomaly scan (can only be confirmed after delivery of the baby). Follow-up 20/02/2014: Diagnosis: Congenital cystic adenomatous malformation of lung in baby. CCAM detected on routine fetal anomaly scan at 20 weeks gestation. Subsequently confirmed when child was born. Child underwent uncomplicated thoracoscopic left lower lobectomy in May 2013. Subsequent follow-up appointment confirms he is well.	Congenital anomaly/birth defect	Obesity	Unrelated	No	Completely recovered	17MAY2013
12006	METFORMIN	13FEB2012	11FEB2012	Stillbirth at term. IUGR - 2610g	Patient died	Maternal Medical History - Osteogenesis inperfecta type 1	Unrelated	No	Death	.
12053	METFORMIN	02SEP2013	02JUN2013	Diagnosis: ?Stillbirth / Neonatal Death. Description: Patient admitted to LW in spontaneous labour. Proceeded to NBFD of female infant. Apgars 0 1. 0 5. 0 10. ?Trisomy 21. ?stillbirth / NND. Severity: Severe	Patient died| Congenital anomaly/birth defect		Unrelated	No	Condition still present and unchanged| Death	.
12056	METFORMIN	30MAY2013	25APR2013	Stillbirth. Description: Cardiac abnormality noted on USS for fetus. SVD of female infant - stillbirth. Severity: Severe	Patient died| Congenital anomaly/birth defect		Unrelated	No	Death	.
12083	METFORMIN	08MAY2014	12MAR2014	Diagnosis: Surgery to correct pyloric stenosis. Description: Baby self-referred by parents to A&E with vomiting and dehydration. H/O since 7 days old of vomiting post feeds. 13/3/14 surgery - Ramstedt's Pyloromyotomy. Discharged home 16/3/14. No flu . Seen 7/5/14 at visit 9. All well. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	07MAY2014
12093	METFORMIN	03APR2014	30MAR2014	Diagnosis: Poor Apgars. ?Infection. Description: Prolonged rupture of membranes - thick meconium at delivery. Poor apgars commenced on IV antibiotics. Blood cultures negative after 36hrs. CRP < 3 on 01/04/2014. Baby discharged home 01/04/2014. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	01APR2014
13147	METFORMIN	14AUG2012	22MAY2012	Diagnosis: Baby diagnosed with PKU Description: Baby diagnosed with PKU on routine blood screening at a week to ten days old. Severity: Severe	Congenital anomaly/birth defect		Unrelated	Yes	Recovered with sequelae	01JUN2012
13528	METFORMIN	05APR2013	24MAR2013	Neonatal hypospadias with chordee. Description: Normal vaginal delivery of male infant at 36+2 (IOL for APH) on 24.3.13. Neonatal hypospadias with chordee noted on paediatric examination. Baby otherwise well and PU'ing as normal. Referred to urology at Alder Hey for follow-up. Follow-up 04/04/2014: Baby diagnosed with hypospadias and referred to Children's hospital for urology follow-up. Severity: Moderate.	Congenital anomaly/birth defect| Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Missing	.
13670	METFORMIN	26JUL2013	21JUL2013	Diagnosis: Bilateral undescended testes. Description: Baby diagnosed with bilateral undescended testes. Baby born via normal vaginal delivery on 21/07/13. Undescended testes noted on 1st exam of the newborn. conducted by community midwife at home on 23/7/13. Baby otherwise well. referred to Alder Hey for follow-up. Severity: Moderate	Congenital anomaly/birth defect		Unrelated	No	Recovered with sequelae	26JUL2013
21095	METFORMIN	21MAR2014	20MAR2014	Diagnosis: No diagnosis yet. Description: Baby transferred to neonatal unit jittery/poor feeding/low BMS. Informed by paed. had significantly low BM's/hypoglycaemia. Raised lactate levels. Septic screen. Severity: Moderate.	Other significant medical events (as defined in protocol)| Involved or prolonged inpatient hospitalisation	Depression (Parent) prior to pregnancy. ongoing. medication required. Urine Infection (Parent). 17/03/2014. ongoing. medication required.	Possibly	No	Completely recovered	23MAR2014
21099	METFORMIN	21MAR2014	15MAR2014	Diagnosis: Significant Neonatal Jaundice. Description: Baby admitted from home to paediatric ward with significant neonatal jaundice. Phototherapy treatment required. Severity: Severe.	Involved or prolonged inpatient hospitalisation| Other significant medical events (as defined in protocol)	Raised BP (Parent). 06/03/2014 - 12/03/2014. no medication required.	Unrelated	No	Completely recovered	18MAR2014
25135	METFORMIN	09JUL2013	08JUL2013	Diagnosis: Congenital Malformation. Description: Circular thoracic lumbar spine lesion. Central 1 x 0.5cm vascular area. within 3 x 1cm area of hypopigmentation. (No hair). ? vascular malformation / occult spinal dysraphism. Follow-up 12/11/13: Diagnosis of Aplasia Cutis Congenita made 11/09/13. Severity: Mild Follow-up 28/01/14: Dermatologist reports evidence of Livedo. more likely livedo racemosa. Investigating for systemic connective tissue disease and full lupus screen. Mother reported (09/01/14) clonus in all 4 limbs of infant therefore referred to neurologist to investigate any central nervous system vasculopathy or abnormality. Severity: Moderate.	Congenital anomaly/birth defect		Possibly	No	Condition still present and unchanged	.

Section 13. Serious Adverse Events

13.2.2 SAE related to the babies - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
25180	METFORMIN	25OCT2013	15OCT2013	Diagnosis: Aortic Stenosis. Description: Mother reported today that an ECG performed at Sheffield Children's Hospital on 15/10/13 had shown an abnormality. F.U. appointment today (25/10/13) in Sheffield. Mother reported she had been told Aortic Stenosis was evident. No actual hard copy reports yet seen by research staff. Will seek to obtain ASAP. Severity: Moderate Follow-up 05/11/13: Diagnosis (Mild to moderate aortic stenosis) confirmed by Echo. Severity: Mild Follow-up 28/01/14: Cardiology review by Dr JD Thomson at Sheffield Northern Hospital (working out of Children's Heart Unit in Leeds) in Dec 2013 concluded Aortic Stenosis more significant than previously presented and at 'Moderate Plus Range'. Likely to require intervention in first year of life. Severity: Moderate.	Congenital anomaly/birth defect		Unrelated	No	Condition still present and unchanged	.
25180	METFORMIN	11SEP2013	08SEP2013	Diagnosis: Mildly dilated lateral posterior ventricular horns seen on cephalic ultrasound scan of infant of participant on 10/09/13. Description: Postnatal scan performed to follow-up antenatal scans showing ventricular measurements at upper end of normal range. Severity: Mild.	Congenital anomaly/birth defect		Possibly	No	Condition still present and unchanged	.
25459	METFORMIN	29JAN2014	28JAN2014	Diagnosis: Left unilateral talipes. Description: Had anomaly scan at 20 weeks gestation - the baby was noted to have left unilateral talipes. Severity: Moderate. Follow-up 01/07/14: Diagnosis: Fixed Talipes left foot. Fixed talipes. Back/hips normal. Initial ponseti plaster applied. To be replaced weekly and continue correction programme. Detected on 20/40 anomaly scan. Severity: Moderate.	Congenital anomaly/birth defect	Mother: Right adrenal cyst. started 15/11/2013. ongoing.	Possibly	No	Condition still present and unchanged	.
11295	PLACEBO	01FEB2012	31JAN2012	Diagnosis: Congenital cardiac defect Description: Major complex cardiac defect diagnosed on fetal anomaly scan on 31/1/12 - double outlet right ventricle. VSD. transposition of the great arteries. likely pulmonary stenosis. Severity: Severe Follow-up 20/02/14: Diagnosis: Tetralogy of Fallot in fetus/baby. Tetralogy of Fallot detected on routine anomaly scan. Baby monitored after birth and continues to be followed up by the paediatric cardiology clinic. Corrective surgery is planned for Spring 2014.	Congenital anomaly/birth defect	Obesity	Unrelated	No	Condition still present and unchanged	.
11536	PLACEBO	17JUN2013	09MAR2013	Diagnosis: Infection. SVT. Description: baby admitted to RHSC. Edinburgh at 8 days old. diagnosed with an infection at that time. At 12 days old diagnosed with SVT. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	23MAR2013
11786	PLACEBO	28APR2014	04NOV2013	Diagnosis: Premature Birth. Description: Born by spontaneous vaginal breech delivery at 30+1 weeks gestation following spontaneous rupture of membranes at 25 weeks gestation. Admitted to neonatal intensive care unit at RIE until 19/11/13 then transferred to Special Care baby Unit at St John's Hospital Livingston until 27/11/13 then transferred to the Royal Hospital for Sick Children. Edinburgh for surgery on inguinal herniae. Discharged on 18/01/14. Has had several readmissions to SJH for problems with feeding and suboptimal weight gain. Has a persistent patent ductus arteriousus and has recently been referred to Yorkhill Hospital Glasgow for surgical repair of this. This is a complication of prematurity. not a congenital anomaly. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Condition still present and unchanged	.
11851	PLACEBO	08APR2014	03APR2014	Diagnosis: Right testicular hydrocele. abnormal left testicle. Description: Right testicular hydrocele. abnormal left testicle. Awaiting ultrasound scan and paediatric surgical review. Severity: Mild.	Congenital anomaly/birth defect		Unrelated	No	Condition still present and unchanged	.
12016	PLACEBO	10SEP2012	21APR2012	Diagnosis: Meconium Aspiration 1. Meconium Aspiration 2. Persistent Pulmonary Hypertension Severity: Severe	Involved or prolonged inpatient hospitalisation| Life-threatening		Unrelated	No	Completely recovered	28APR2012
12039	PLACEBO	16APR2013	24MAR2013	Diagnosis: Respiratory Distress. Description: Baby admitted to SCBU following EMCS for respiratory distress and ? sepsis. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	28MAR2013
12059	PLACEBO	16SEP2013	28JUN2013	Diagnosis: IUGR. Description: Baby admitted to SCBU following C-section due to IUGR and absent EDF. Delivery at 33+3 weeks. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	18JUL2013
12092	PLACEBO	23JUL2014	11JUN2014	Diagnosis: Upper respiratory infection. Viral gastroenteritis. Admitted to children's accident and emergency department with a history of pyrexia and being unsettled and decreased feeding. Lumbar puncture performed. IV antibiotics. IV fluids. Urine NAD. Blood cultures negative. Rhinovirus and entrovirus positive. No physio needed. CSF negative. discharged home 14/06/2014. No follow-up. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	23JUL2014
12111	PLACEBO	22AUG2014	02JUN2014	Diagnosis: weight loss and urinary tract infection Description: attended accident and emergency with vomiting after feeds and weight loss. Commenced on IV antibiotics as urine nitrite positive. treated for urinary tract infection. Allowed home on leave between IV antibiotic doses 04/06/14. Urine pure growth of e.coli. Discharged home 04/06/14 with 7 days of trimethoprim. No follow up needed Severity: moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	19AUG2014

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DOI: 10.3310/eme03070

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Section 13. Serious Adverse Events

13.2.2 SAE related to the babies - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
13496	PLACEBO	14FEB2013	11FEB2013	Diagnosis: Baby admitted to NICU for low blood glucose Description: EH diagnosed as gestational diabetic at 36 weeks. managed on diet control only. Had elective caesarian section on 11.02.13 at 11am. Baby cord blood 2.4mmol. was grunting and had low TBG's on ward. Was admitted to NICU at 22.35 hours 11.02.13. Discharged back to ward with mum at 14.15 the next day 12.02.13. Mum and baby discharged home 13.02.13 baby asymptomatic of hypoglycaemia and BF well on discharge. No anticipated follow up. Severity: Mild	Involved or prolonged inpatient hospitalisation		Possibly	Yes	Completely recovered	13FEB2013
13591	PLACEBO	26JUL2013	20APR2013	Date of onset: ?? 20/04/2013 (i.e. from 2 weeks old - see below). Diagnosis: Baby developed vascular malformation. Description: Baby diagnosed with a venous malformation on upper shoulder. The baby was born on 6th April and nil was noted at birth or on the first paediatric examination. At the 6 week postnatal check with the GP a birth mark was noted and thought to be a haemangioma of infancy. I saw mum at 3 month postnatal visit on 4th July, when I first became aware of the birth mark. but as it wasn't picked up until the baby was 6 weeks old. this was outside of the 28 day postnatal reporting period for EMPOWaR. Mum has since been in touch to say that the birth mark has now been diagnosed as a venous malformation as it is the blood vessels below the actual mark which are causing it to grow and cause a lump. On further questioning mum thinks that the mark may have been there since 2 weeks of life but initially very small. Baby has been referred to a specialist at Alder Hey for management and possible removal	Congenital anomaly/birth defect	See previous SAE dated 7.5.13: Mother had hospital admission for gall stones at 24 days post natal. Having follow up at Royal Liverpool Hospital.	Unrelated	No	Recovered with sequelae	26JUL2013
14145	PLACEBO	18JUN2012	18JUN2012	Date of onset: 18.06.12 (cardiac anomalies found on ultrasound). Initial: Fetus has transposition of the great arteries with a ventricular septal defect and suspected coarctation of the aorta. Fetal echocardiogram done at Leeds General Infirmary on 15.06.12. Follow-up: Baby was born at Leeds General Infirmary (LGI) as he was known to have a serious cardiac anomaly 9SAE sent at the time). Baby died on 19h October 2012 at LGI. According to his mum (the study participant) this was due to infection following major cardiac surgery. I am awaiting confirmation of these details from the research midwives at LGI and will forward them to you asap.	Congenital anomaly/birth defect	Participant (mother) changed from the study drug (either Metformin or Placebo) to Metformin on 01.09.12. She had been admitted to hospital in threatened premature labour and had forgotten to take her study drugs with her. She was prescribed Metformin by t	Unrelated	No	Death	.
14413	PLACEBO	03MAR2014	03MAR2014	Diagnosis: Baby delivered with some abnormalities. Description: C/section at 3/3/14 at 12.30 - baby found to have abnormal toes. fingers and anteriorly placed anus. Left hand is normal. Right hand has a middle short finger with hypoplastic nail and is twisted. Index finder has an accessory digit. On the right foot the big toe has syndactyly and the 3rd toe is not formed. On the left foot. the big toe is syndactyly and the 3rd toe not formed. There is only one centimetre between the anus and the posterior forchette. Severity: Severe.	Congenital anomaly/birth defect		Unrelated	No	Condition still present and unchanged	.
15028	PLACEBO	17JUN2013	17JUN2013	Diagnosis: Neonatal Death on day 5. Male infant. Description: Neonatal death of infant on day 5 (born 13/06/2013). Baby born at 28+4 weeks of gestation. Preterm rupture of membranes confirmed at 20+4 weeks gestation. Severity: Severe	Patient died	Gestational Diabetes 13/06/2013	Unrelated	No	Death	.
16212	PLACEBO	08JAN2014	04JAN2014	Diagnosis: VSD/ASD/PFO on echo. Description: Perimembranous ventricular septal defect with a L-R shunt. 2 x L-R shunt in the patent foramen ovale/Ft cundum region of the atrial septum. Severity: Mild.	Congenital anomaly/birth defect		Unrelated	No	Condition still present and unchanged	.
21018	PLACEBO	05NOV2013	17OCT2013	Diagnosis: Presumed Sepsis/Pneumonia consolidation. Description: Admitted to neonatal unit shortly after birth for investigations for spreading vascular lesions on truck. grunting and tachypnoeic. Remained on neonatal unit 17 - 22/10/13. Severity: Moderate	Involved or prolonged inpatient hospitalisation	Vascular lesions. grunting. tachypnoeic. pneumonia. started 17/10/2013. ended 22/10/2013. medication required.	Unrelated	No	Completely recovered	24OCT2013
21038	PLACEBO	16JAN2014	31DEC2013	Diagnosis: Cyanotic episodes. likely vasomotor phenomenon. Description: Admitted to ward 8 via ambulance/A&E 7 days old with cyanotic episodes 10 times a day lasting 3 - 5 mins. Investigations all normal. Discharged home 02/01/2014. No further admissions. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	02JAN2014

Section 13. Serious Adverse Events

13.2.2 SAE related to the babies - Details

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*SAE - date of report*	*SAE - date of event*	*Description of SAE*	*Expedited Reporting Criteria*	*Relevant History*	*SAE_related_coded*	*SAE_expected_coded (Y/N)*	*SAE_outcome_coded*	*SAE - date of recovery*
21047	PLACEBO	22APR2014	22JAN2014	Diagnosis: RSV positive bronchiolitis. Description: Admitted to paediatric ward at 2 weeks old with cough and increased work of breathing. Required oxygen and help with NG feeds for a few days. Gradually recovered. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Gestational Diabetes (Mother). 17/12/2013 - 08/01/2014.	Unrelated	No	Completely recovered	30JAN2014
21069	PLACEBO	19MAR2014	18FEB2014	Diagnosis: Meningitis/Sepsis. Description: Admitted to Neonatal Unit shortly after birth jittery/maternal sepsis. Had dusky episodes/desaturations/apnoeas/jaundice/sepsis. Ventilated. Meningitis diagnosed. / Cerebral Haemorrhage. Severity: Severe.	Involved persistent or significant disability or incapacity| Involved or prolonged inpatient hospitalisation	Sepsis in labour/maternal infection (Parent). 18/02/2014 - 25/02/2014. medication required.	Unrelated	No	Completely recovered	07MAR2014
21119	PLACEBO	06JAN2014	02JAN2014	Diagnosis: Congenital Anomaly. Description: Anomaly ultrasound scan showed structural abnormalities to hands and feet. Appearances suggestive of split hand and foot syndrome. Severity: Severe	Patient died| Congenital anomaly/birth defect		Unrelated	No	Death	.
25320	PLACEBO	03FEB2014	31JAN2014	Diagnosis: ? Hirschsprungs in neonate. Description: Distended stomach on antenatal scans. At birth neonate admitted to NNU then transfer to tertiary centre same day (Nottingham Queen's Medical). Severity: Severe. Follow-up 27/02/2014: Subsequently resolved. no pathology. baby discharged. Severity: Severe.	Congenital anomaly/birth defect		Unrelated	No	Completely recovered	27FEB2014

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DOI: 10.3310/eme03070 EFFICACY AND MECHANISM EVALUATION 2016 VOL. 3 NO. 7

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EMPOWaR: Efficacy of Metformin in Pregnant Obese Women, a Randomised Controlled Trial

Funding reference number: 08/246/09 (NIHR Efficacy and Mechanism Evaluation Programme)
EudraCT number 2009-017134-47

Statistical Report

Population = Per-Protocol (PP) - AllocatedTreatment used for analysis

Report number: 02

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Data set analysed as it was on:
29 April 2015

EMPOWaR Statistical Report (AllocatedTreatment used) - tables run on: 05MAR2016

By: Aryelly Rodriguez - ECTU Statistician

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Section 1. Disposition / data checks

1.1 Patient disposition before randomisation - All Centres

Parameter(s)	*Categories*	*---Overall--- Count (n(%)*
All patients in DB (n(%))	Yes	4867 (100)
Declined reason (n(%))	Subject participate has declined	2861 (58.8)
	Other Reason	57 (1.2)
	Failed Exclusion	100 (2.1)
	Failed Inclusion	626 (12.9)
	Failed both Exclu and Inclu	4 (0.1)
	Did not decline and pass IN_EX but not rand*	10 (0.2)
	Did not attend appointment	8 (0.2)
	Unable to contact	752 (15.5)
	Did not decline and pass IN_EX and rand	449 (9.2)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
n = number of observations
*These patients (13045 13053 13084 13102 13117 13121 13122 13123 13168 13189) were screened as eligible, but then they subsequently declined or were no longer contactable
NOTE:These patients (11562 11892 13047 13065) were randomised but also have a reason to decline

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Section 1. Disposition / data checks

1.2.1.1 Patient disposition after randomisation - All Centres

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Consented/randomised (n(%))	Yes	118 (100)	109 (100)	227 (100)
Disposition in database (n(%))	Active	116 (98.3)	107 (98.2)	223 (98.2)
	Lost to follow up	1 (0.8)	0	1 (0.4)
	Participant withdrawn	1 (0.8)	2 (1.8)	3 (1.3)
Outcome (z score) available* (n(%))	Yes - Live Birth	117 (99.2)	108 (99.1)	225 (99.1)
	No - Termination of Pregnancy	1 (0.8)	0	1 (0.4)
	No - Not available	0	1 (0.9)	1 (0.4)
Outcome (Glucose test) avalilable# (n(%))	Yes	103 (87.3)	92 (84.4)	195 (85.9)
	No	15 (12.7)	17 (15.6)	32 (14.1)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = number of observations

*Available at visit 8 (Delivery) - the latest date of delivery (DOD) was 14JUL2014, for Patient 13508 outcome was miscarriage and for Patient 12074 outcome was alive birth, these labels were assigned post database lock

#Available at visit 6 (36 Weeks) - checks: test date, base value and two hr value must be present

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Section 1. Disposition / data checks

1.2.1.2 Patient disposition after randomisation - All Centres - Consort figures

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Treatment distributed(n(%))	Data available	118 (100)	109 (100)	227 (100)
Outcome (z score) available* (n(%))	Data available	117 (99.2)	108 (99.1)	225 (99.1)
	Withdrawn post treatment	0	1 (0.9)	1 (0.4)
	Termination of Pregnancy	1 (0.8)	0	1 (0.4)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
N = number of patients randomised, n = number of observations
*Available at visit 8 (Delivery)
IMPORTANT NOTES on manual identification:
Patients 12046 and 12047 withdrawn pre treatment
Patients 17063, 27317 and 18113 withdrawn post treatment
Patients 12041, 12086 and 21119 were identified as miscarriage but they were termination of pregnacies TOP

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Section 1. Disposition / data checks

1.2.1.2 Patient disposition after randomisation - All Centres - Consort figures (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Follow up Visit 9 data available* (n(%))	Data available	90 (76.3)	91 (83.5)	181 (79.7)
	Did not attend the visit	25 (21.2)	16 (14.7)	41 (18.1)
	Decline to further participate	1 (0.8)	1 (0.9)	2 (0.9)
	Lost to follow up	1 (0.8)	0	1 (0.4)
	Withdrawn post treatment	0	1 (0.9)	1 (0.4)
	Termination of Pregnancy	1 (0.8)	0	1 (0.4)

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Section 1. Disposition / data checks

1.2.2 Study Populations - All Centres

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Randomised - ITT population (n(%))*	Yes	223 (100)	226 (100)	449 (100)
IMP at least once (n(%))#	Missing	46	59	105
	No	8 (4.5)	9 (5.4)	17 (4.9)
	Yes	169 (95.5)	158 (94.6)	327 (95.1)
Compliant - PP population (n(%))$	Missing	46	59	105
	No	59 (33.3)	58 (34.7)	117 (34.0)
	Yes	118 (66.7)	109 (65.3)	227 (66.0)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47
N = number of patients randomised, n = number of observations
*The intention to treat (ITT) population will comprise all randomised subjects
#Members of the ITT population who took IMP at least once
$The per-protocol (PP) population will comprise those members of the ITT population who completed the study without a major protocol violation and who complied adequately with the randomised treatment, further details of treatment compliance are in table 3.2.2 of this report

By: Aryelly Rodriguez - ECTU Statistician

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Section 1. Disposition / data checks

1.3 Patient disposition - Minimisation variables

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Centres (n(%))	Royal Infirmary of Edinburgh	32 (27.1)	36 (33.0)	68 (30.0)
	Coventry	14 (11.9)	8 (7.3)	22 (9.7)
	Liverpool Womens Hospital	26 (22.0)	19 (17.4)	45 (19.8)
	Sheffield	11 (9.3)	7 (6.4)	18 (7.9)
	Notts City	3 (2.5)	4 (3.7)	7 (3.1)
	Notts QMC	5 (4.2)	5 (4.6)	10 (4.4)
	Bradford	3 (2.5)	3 (2.8)	6 (2.6)
	St Helens	1 (0.8)	2 (1.8)	3 (1.3)
	Chelsea and Westminster	0	1 (0.9)	1 (0.4)
	Preston	15 (12.7)	15 (13.8)	30 (13.2)
	Arrow Park Wirral	0	1 (0.9)	1 (0.4)
	Chesterfield	8 (6.8)	8 (7.3)	16 (7.0)
BMI band at randomisation*(n(%))	30-39 Kg/m^2	80 (67.8)	73 (67.0)	153 (67.4)
	>40 Kg/m^2	38 (32.2)	36 (33.0)	74 (32.6)

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N = number of patients randomised, n = number of observations

*For patients 11693 and 17059, BMI was calculated at randomisation using the height in m instead of cm, as a consequence the results were respectively 375390 and 352955 kg/m^2 and these patients landed in the >40 kg/m^2 BMI band, their calculated BMI were 37.5 and 35.50 kg/m^2

Section 1. Disposition / data checks

1.4 Data Completeness by time point

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Patients CRF Completeness by CRF SECTIONS	Allocated Regimen: METFORMIN Visit attended		PLACEBO Visit attended	
	Yes	No	Yes	No
VISIT 1 (SCREENING)	109	0	118	0
VISIT 2 (BASELINE)	109	0	118	0
VISIT 3 (RANDOMISATION)	109	0	118	0
VISIT 4 (18 TO 20 WEEKS)	108	1	115	3
VISIT 5 (28 WEEKS)	109	0	117	1
VISIT 6 (36 WEEKS)	96	13	107	11
VISIT 7 (TERM)	52	57	55	63
VISIT 8 (DELIVERY)	106	3	115	3
VISIT 9 (FINAL)	91	18	90	28

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Section 1. Disposition / data checks

1.4 Data Completeness by time point

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Patients CRF Completeness by CRF SECTIONS	*Allocated Regimen* OVERALL *Visit attended*	
	Yes	*No*
VISIT 1 (SCREENING)	227	0
VISIT 2 (BASELINE)	227	0
VISIT 3 (RANDOMISATION)	227	0
VISIT 4 (18 TO 20 WEEKS)	223	4
VISIT 5 (28 WEEKS)	226	1
VISIT 6 (36 WEEKS)	203	24
VISIT 7 (TERM)	107	120
VISIT 8 (DELIVERY)	221	6
VISIT 9 (FINAL)	181	46

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.1 Maternal Age

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Maternal Age at consent (years)	Mean	29.6	29.8	29.7
	Median	29.0	30.0	30.0
	SD	5.0	5.6	5.3
	MIN,MAX	20,43	19,42	19,43
	Q1,Q3	26,33	25,34	25,34
	n	118	109	227
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.2 Maternal Life Style Status

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Smoking Status (n(%))	ACTIVE	13 (11.0)	13 (11.9)	26 (11.5)
	PREVIOUSLY	6 (5.1)	6 (5.5)	12 (5.3)
	NOT SMOKING	99 (83.9)	90 (82.6)	189 (83.3)
Alcohol During Pregnancy (n(%))	Yes	6 (5.1)	0	6 (2.6)
	No	112 (94.9)	109 (100)	221 (97.4)
Illicit Drug Status (n(%))	NOT USING	118 (100)	109 (100)	227 (100)

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.3 Maternal Education

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Educational Qualifications (n(%))	No formal qualifications	8 (6.8)	3 (2.8)	11 (4.8)
	Entry level certification/foundation diploma	2 (1.7)	5 (4.6)	7 (3.1)
	GCSE, Standard grade, "O" grades	27 (22.9)	18 (16.5)	45 (19.8)
	A level, A/S level, Highers or BTEC Dip/Cert.	21 (17.8)	15 (13.8)	36 (15.9)
	Cert. higher Education, City & Guilds	9 (7.6)	9 (8.3)	18 (7.9)
	Diploma HE/FE or HND/HNC	19 (16.1)	14 (12.8)	33 (14.5)
	Graduate certificate or Diploma	2 (1.7)	5 (4.6)	7 (3.1)
	Degree	20 (16.9)	35 (32.1)	55 (24.2)
	Professional Qualification	2 (1.7)	2 (1.8)	4 (1.8)
	PGCE/Postgraduate certificate or Diploma, Masters. Doctorate	8 (6.8)	3 (2.8)	11 (4.8)
Educational Qualifications coded (n(%))	None	8 (6.8)	3 (2.8)	11 (4.8)
	School up to 16 years	29 (24.6)	23 (21.1)	52 (22.9)
	School 16 to 18 years	30 (25.4)	24 (22.0)	54 (23.8)
	College or Uni degree or Higher	51 (43.2)	59 (54.1)	110 (48.5)

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.4.1 Previous pregnacy status* PARITY 1

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
PARITY1 (n(%))	0	44 (37.3)	54 (49.5)	98 (43.2)
	=>1	74 (62.7)	55 (50.5)	129 (56.8)

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.4.2 Previous pregnacy status*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Number of Previous Pregnancies (n(%))	0	31 (26.3)	41 (37.6)	72 (31.7)
	1	41 (34.7)	28 (25.7)	69 (30.4)
	2	22 (18.6)	18 (16.5)	40 (17.6)
	3	10 (8.5)	12 (11.0)	22 (9.7)
	4	6 (5.1)	5 (4.6)	11 (4.8)
	5	6 (5.1)	1 (0.9)	7 (3.1)
	6	1 (0.8)	1 (0.9)	2 (0.9)
	7	1 (0.8)	2 (1.8)	3 (1.3)
	8	0	1 (0.9)	1 (0.4)
At least one Prev Preg* (n(%))	Yes	87 (73.7)	68 (62.4)	155 (68.3)
	No	31 (26.3)	41 (37.6)	72 (31.7)

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N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 12 weeks or more were considered regardless of outcome and if a patient had more than one previous pregnancy, only her latest pregnancy was counted

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.4.3 Previous Pregnancy details*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Multiple Pregnancy#(%)	Yes	2 (2.3)	1 (1.5)	3 (1.9)
	No	85 (97.7)	67 (98.5)	152 (98.1)
Gestation of Pregnancy#(weeks)(n(%))	<12	21 (24.1)	19 (27.9)	40 (25.8)
	12<22	0	3 (4.4)	3 (1.9)
	>22	66 (75.9)	46 (67.6)	112 (72.3)
Last Pregnancy Outcome#(%)	Miscarriage	15 (17.2)	18 (26.5)	33 (21.3)
	Ectopic	1 (1.1)	1 (1.5)	2 (1.3)
	Termination of Pregnancy	5 (5.7)	3 (4.4)	8 (5.2)
	Live Birth	66 (75.9)	46 (67.6)	112 (72.3)
Pre term Birth#(n(%))	Missing	13	16	29
	Yes	3 (4.1)	2 (3.8)	5 (4.0)
	No	71 (95.9)	50 (96.2)	121 (96.0)

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N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 12 weeks or more were considered regardless of outcome and if a patient had more than one previous pregnancy, only her latest pregnancy was counted

#Only summarised for patiens who has a previous pregnancy in the previous table

Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.5 Maternal Blood Pressure at baseline

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Maternal Systolic BP (mmHg)	Mean	119.3	117.1	118.3
	Median	120.0	118.0	119.0
	SD	11.2	11.3	11.3
	MIN,MAX	100,142	91,148	91,148
	Q1,Q3	110,129	110,124	110,127
	n	118	109	227
	Nmiss	0	0	0
Maternal Diastolic BP (mmHg)	Mean	69.0	68.5	68.8
	Median	69.5	70.0	70.0
	SD	7.7	7.9	7.8
	MIN,MAX	54,90	49,86	49,90
	Q1,Q3	64,74	60,74	61,74
	n	118	109	227
	Nmiss	0	0	0

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

2.1.6 Current pregnancy details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Ultrasound Confirmation (n(%))	Yes	117 (99.2)	109 (100)	226 (99.6)
	No	1 (0.8)	0	1 (0.4)
Gestation at baseline* (days)	Mean	98.9	100.0	99.4
	Median	100.0	100.0	100.0
	SD	9.0	7.9	8.5
	MIN,MAX	71,112	74,112	71,112
	Q1,Q3	92,106	95,107	94,107
	n	118	109	227
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Gestation at this time point shold be between 70 and 112 days

Section 2. Baseline - Visit 2 (10-16 Weeks) - Putative father

2.2.1 Putative father Age

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Paternal age (years)	Mean	32.3	32.0	32.2
	Median	32.0	32.0	32.0
	SD	6.2	6.0	6.1
	MIN,MAX	15,50	21,46	15,50
	Q1,Q3	28,36	27,37	28,36
	n	117	108	225
	Nmiss	1	1	2

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Putative father

2.2.2 Putative father Height and Weight

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Paternal height (cm)	Mean	178.5	177.9	178.2
	Median	178.0	178.0	178.0
	SD	7.8	13.2	10.7
	MIN,MAX	156,200	76,196	76,200
	Q1,Q3	173,183	174,185	174,183
	n	107	100	207
	Nmiss	11	9	20
Paternal weight (Kg)	Mean	92.1	94.6	93.3
	Median	89.7	89.0	89.1
	SD	21.9	27.7	24.8
	MIN,MAX	57,148	57,196	57,196
	Q1,Q3	74,105	77,108	76,107
	n	102	95	197
	Nmiss	16	14	30

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 2. Baseline - Visit 2 (10-16 Weeks) - Putative father

2.2.3 Putative father Ethnicity

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Ethnic Origin (n(%))	White	114 (96.6)	101 (92.7)	215 (94.7)
	Non-White	4 (3.4)	8 (7.3)	12 (5.3)
Ethnic Origin-More detail (n(%))	White	114 (96.6)	101 (92.7)	215 (94.7)
	Mixed	1 (0.8)	2 (1.8)	3 (1.3)
	Asian	0	2 (1.8)	2 (0.9)
	Black	2 (1.7)	3 (2.8)	5 (2.2)
	Othe Ethnic group	1 (0.8)	1 (0.9)	2 (0.9)

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Medical history

2.3.1 Preeclampsia or Hypertension / Hypertension Requiring Treatment

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Preeclampsia or Hypertension (n(%))	Yes	3 (2.5)	6 (5.5)	9 (4.0)
	No	115 (97.5)	103 (94.5)	218 (96.0)
Currently taking Medication (n)	No	3	6	9
Hypertension Require Treatment (n(%))	Yes	1 (0.8)	1 (0.9)	2 (0.9)
	No	117 (99.2)	108 (99.1)	225 (99.1)
Currently taking Medication (n)	No	1	1	2

Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Medical history

2.3.2 Polycystic Ovarian Syndrome / Depression Requiring Treatment

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Polycystic Ovarian Syndrome (n(%))	Yes	14 (11.9)	16 (14.7)	30 (13.2)
	No	103 (87.3)	92 (84.4)	195 (85.9)
	Unk	1 (0.8)	1 (0.9)	2 (0.9)
Currently taking Medication (n)	No	14	16	30
Depression Require Treatment (n(%))	Yes	33 (28.0)	24 (22.0)	57 (25.1)
	No	85 (72.0)	85 (78.0)	170 (74.9)
Currently taking Medication (n)	Yes	5	4	9
	No	28	20	48

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Medical history

2.3.3 Anxiety Requiring Treatment / Use of Steriods

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Anxiety Require Treatment (n(%))	Yes	7 (5.9)	7 (6.4)	14 (6.2)
	No	111 (94.1)	102 (93.6)	213 (93.8)
Currently taking Medication (n)	Yes	2	1	3
	No	5	6	11
Use of Steriods (n(%))	Yes	12 (10.2)	7 (6.4)	19 (8.4)
	No	106 (89.8)	102 (93.6)	208 (91.6)
Currently taking Medication (n)	Yes	12	7	19

Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother Family history

2.4 Any family history for the following conditions

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Medical History* (n(%))	Yes	73 (61.9)	76 (69.7)	149 (65.6)
	No	42 (35.6)	32 (29.4)	74 (32.6)
	Unk	3 (2.5)	1 (0.9)	4 (1.8)
Cardiovascular disease (n(%))	Yes	41 (34.7)	31 (28.4)	72 (31.7)
	No	74 (62.7)	77 (70.6)	151 (66.5)
	Unk	3 (2.5)	1 (0.9)	4 (1.8)
Diabetes(n(%))	Yes	54 (45.8)	47 (43.1)	101 (44.5)
	No	62 (52.5)	61 (56.0)	123 (54.2)
	Unk	2 (1.7)	1 (0.9)	3 (1.3)
Preeclampsia(n(%))	Yes	8 (6.8)	4 (3.7)	12 (5.3)
	No	107 (90.7)	102 (93.6)	209 (92.1)
	Unk	3 (2.5)	3 (2.8)	6 (2.6)
Any other medical history(n(%))	Yes	58 (49.2)	57 (52.3)	115 (50.7)
	No	60 (50.8)	52 (47.7)	112 (49.3)

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N = number of patients randomised, n = number of observations

*In order to be yes, at least one condition below must be present, for no all conditions below must be also no

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.1 Mother Anthropometry / Height and Weight*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Maternal Height (cm)	Mean	166.1	165.8	166.0
	Median	166.2	165.5	166.0
	SD	6.0	5.7	5.9
	MIN,MAX	152,184	153,180	152,184
	Q1,Q3	162,170	162,170	162,170
	n	118	109	227
	Nmiss	0	0	0
Maternal Weight (kg)	Mean	103.74	104.04	103.88
	Median	98.33	104.00	101.30
	SD	16.95	15.22	16.10
	MIN,MAX	75.6,154.0	74.0,140.3	74.0,154.0
	Q1,Q3	90.6,114.6	93.3,115.0	92.0,115.0
	n	118	109	227
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.2 Mother Anthropometry / BMI_c and Waist*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Maternal BMI Calculated (kg/m^2)	Mean	37.549	37.782	37.661
	Median	36.583	37.494	37.036
	SD	5.462	4.708	5.104
	MIN,MAX	30.23,52.79	30.08,47.87	30.08,52.79
	Q1,Q3	33.14,41.25	34.27,41.45	33.56,41.28
	n	118	109	227
	Nmiss	0	0	0
Maternal Waist (cm)	Mean	108.32	108.57	108.44
	Median	106.00	108.60	107.00
	SD	12.58	11.20	11.91
	MIN,MAX	85.0,148.0	84.0,134.0	84.0,148.0
	Q1,Q3	98.5,118.0	100.5,117.0	100.0,117.0
	n	118	109	227
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.3 Mother Anthropometry / Hip and MidArm*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Maternal Hip (cm)	Mean	126.80	127.50	127.14
	Median	125.00	126.00	125.00
	SD	11.58	12.22	11.87
	MIN,MAX	103.5,155.0	100.0,155.0	100.0,155.0
	Q1,Q3	118.0,133.5	119.0,136.0	118.5,134.0
	n	118	109	227
	Nmiss	0	0	0
Maternal Mid Arm (cm)	Mean	36.63	37.05	36.83
	Median	36.00	37.00	36.00
	SD	4.75	4.42	4.59
	MIN,MAX	22.0,48.0	28.0,52.0	22.0,52.0
	Q1,Q3	34.0,39.0	34.0,39.4	34.0,39.0
	n	117	106	223
	Nmiss	1	3	4

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.4 Mother Anthropometry / Mid Thigh and Tricep Skinfold*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Maternal Mid Thigh (cm)	Mean	64.22	65.34	64.75
	Median	64.25	64.00	64.00
	SD	7.31	7.00	7.17
	MIN,MAX	25.0,84.0	50.0,86.0	25.0,86.0
	Q1,Q3	60.0,68.8	61.0,69.0	60.0,69.0
	n	116	106	222
	Nmiss	2	3	5
Maternal Tricep Skinfold (mm)	Mean	33.326	32.564	32.960
	Median	31.200	31.500	31.200
	SD	9.379	9.659	9.501
	MIN,MAX	15.00,62.00	10.00,66.00	10.00,66.00
	Q1,Q3	27.00,40.00	26.00,38.70	26.50,39.00
	n	117	108	225
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 2. Baseline - Visit 2 (10-16 Weeks) - Mother details

2.5.5 Mother Anthropometry / Bicep Skinfold and Subscapular Skinfold*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Maternal Bicep Skinfold (mm)	Mean	27.362	27.824	27.584
	Median	25.000	26.000	25.500
	SD	10.087	10.707	10.369
	MIN,MAX	8.50,60.00	9.00,61.00	8.50,61.00
	Q1,Q3	21.00,32.00	20.00,33.00	20.80,32.40
	n	117	108	225
	Nmiss	1	1	2
Maternal Subscapular Skinfold (mm)	Mean	35.313	34.784	35.059
	Median	34.000	33.000	34.000
	SD	11.026	11.730	11.346
	MIN,MAX	12.00,67.80	9.90,67.00	9.90,67.80
	Q1,Q3	28.00,40.60	26.50,40.00	27.00,40.00
	n	117	108	225
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 3. Compliance

3.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated* Gestation - Visit 1 (days)	Mean	86.2	86.3	86.3
	Median	87.5	88.0	88.0
	SD	14.1	13.6	13.9
	MIN,MAX	51,112	52,112	51,112
	Q1,Q3	76,97	79,95	79,96
	n	118	109	227
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	98.9	100.0	99.4
	Median	100.0	100.0	100.0
	SD	9.0	7.9	8.5
	MIN,MAX	71,112	74,112	71,112
	Q1,Q3	92,106	95,107	94,107
	n	118	109	227
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value, repeated from table 2.1.6, shown here just for completeness

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Section 3. Compliance

3.1 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks) (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated* Gestation - Visit 3 (days)	Mean	101.4	101.6	101.5
	Median	103.0	102.0	102.0
	SD	8.2	7.2	7.7
	MIN,MAX	84,118	85,113	84,118
	Q1,Q3	95,108	97,108	96,108
	n	118	109	227
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	141.6	139.8	140.7
	Median	140.0	140.0	140.0
	SD	11.4	7.6	9.7
	MIN,MAX	108,198	124,166	108,198
	Q1,Q3	136,146	134,143	135,145
	n	116	108	224
	Nmiss	2	1	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 3. Compliance

3.1 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks) (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated* Gestation - Visit 5 (days)	Mean	196.9	197.3	197.1
	Median	197.0	197.0	197.0
	SD	6.7	6.3	6.5
	MIN,MAX	155,224	167,226	155,226
	Q1,Q3	194,200	195,200	194,200
	n	118	109	227
	Nmiss	0	0	0
Calculated* Gestation - Visit 6 (days)	Mean	252.2	253.6	252.9
	Median	253.0	253.5	253.0
	SD	10.3	4.9	8.2
	MIN,MAX	155,263	234,266	155,266
	Q1,Q3	250,256	251,256	251,256
	n	109	102	211
	Nmiss	9	7	16

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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Section 3. Compliance

3.1 Gestation by timepoint - Visit 7 Term (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated* Gestation - Visit 7 (days)	Mean	285.7	277.9	281.8
	Median	276.5	277.0	277.0
	SD	90.8	16.7	65.4
	MIN,MAX	155,1011	250,393	155,1011
	Q1,Q3	273,282	273,281	273,281
	n	68	67	135
	Nmiss	50	42	92
Calculated* Gestation - Visit 8 (days)	Mean	279.9	278.0	279.0
	Median	281.0	278.0	280.0
	SD	21.2	13.2	17.8
	MIN,MAX	155,375	216,337	155,375
	Q1,Q3	273,289	271,285	271,287
	n	118	108	226
	Nmiss	0	1	1

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 3. Compliance

3.1 Gestation by timepoint - Visit 8 Delivery (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Recorded* Gestation - Visit 8 (days)	Mean	276.6	276.6	276.6
	Median	277.5	278.0	278.0
	SD	17.1	11.5	14.7
	MIN,MAX	152,297	219,297	152,297
	Q1,Q3	271,287	271,284	271,285
	n	118	108	226
	Nmiss	0	1	1
Coded R_gestation - Visit 8 (n(%))	Missing	0	1	1
	<= 24 WEEKS	1 (0.8)	0	1 (0.4)
	>24 and <=37 WEEKS	4 (3.4)	8 (7.4)	12 (5.3)
	>37 WEEKS	113 (95.8)	100 (92.6)	213 (94.2)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Actual recorded value

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Section 3. Compliance

3.2.1 Treatment compliance / Tablets returned by study visit

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Tablets Returned Visit 5 (28 Weeks) (n(%))	Missing	20	11	31
	Yes	9 (9.2)	6 (6.1)	15 (7.7)
	No	89 (90.8)	92 (93.9)	181 (92.3)
Tablets Returned Visit 8 (Delivery) (n(%))	Missing	19	9	28
	Yes	53 (53.5)	57 (57.0)	110 (55.3)
	No	46 (46.5)	43 (43.0)	89 (44.7)

Section 3. Compliance

3.2.2 Treatment compliance Calculated using the patient diary (as per SAP)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated Compliance* (n(%))	Yes	118 (100)	109 (100)	227 (100)

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N = number of patients randomised, n = number of observations

*The number of weeks that a patient was pregnant within the study period was calculated using the gestation at baseline and the gestation at delivery, this value was then halved and compared to the number of weeks recorded in the diary, if a patient has less week diary entries than the halved total weeks then she is non-compliant straight away. If a patient had equal or more week diary entries than halved total weeks then it was required that she taken at least one pill for 4 days in order to declare a compliant week. Finally for being treatment compliant the patient should have equal or more than 50% of compliant weeks out of all available weeks

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Section 3. Compliance

3.2.3.1 Cross Check* of Treatment compliance Calculated# vs tablets returned - Visit 5 (28 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Compliance by tablets retuned at visit 5	*Allocated Regimen*			
	METFORMIN		*PLACEBO*	
	Tablets returned		*Tablets returned*	
	Yes	*No*	*Yes*	*No*
Compliance				
Yes	6	92	9	89

Compliance by tablets retuned at visit 5	*Allocated Regimen*	
	OVERALL	
	Tablets returned	
	Yes	*No*
Compliance		
Yes	15	181

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N = number of patients randomised, n = number of observations

*This table is just a compleness check and its outcome did not affect the ITT, safety or the PP population

#Compliance is explained in table 3.2.2 of this report

Section 3. Compliance

3.2.3.2 Cross Check* of Treatment compliance Calculated# vs tablets returned - Visit 8 Delivery

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Compliance by tablets retuned at visit 8	*Allocated Regimen*			
	METFORMIN		*PLACEBO*	
	Tablets returned		*Tablets returned*	
	Yes	*No*	*Yes*	*No*
Compliance				
Yes	57	43	53	46

Compliance by tablets retuned at visit 8	*Allocated Regimen*	
	OVERALL	
	Tablets returned	
	Yes	*No*
Compliance		
Yes	110	89

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N = number of patients randomised, n = number of observations

*This table is just a compleness check and its outcome did not affect the ITT, safety or the PP population

#Compliance is explained in table 3.2.2 of this report

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Section 3. Compliance

3.3 Treatment compliance / Metformin level in blood samples at Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Metformin level (ng/mL)	Mean	1.5	90.8	43.6
	Median	0.0	28.5	0.0
	SD	11.6	210.5	151.1
	MIN,MAX	0,110	0,1611	0,1611
	Q1,Q3	0,0	1,75	0,27
	n	93	83	176
	Nmiss	25	26	51
Any Metformin level coded (n(%))	Missing	25	26	51
	Yes	7 (7.5)	63 (75.9)	70 (39.8)
	No	86 (92.5)	20 (24.1)	106 (60.2)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 3. Compliance

3.4 Cross Check* of Treatment compliance Calculated# vs Metformin level in blood samples at Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Compliance by metformin level at visit 6	Allocated Regimen			
	METFORMIN		PLACEBO	
	Any Metformin		Any Metformin	
	Yes	No	Yes	No
Compliance				
Yes	63	20	7	86

Compliance by metformin level at visit 6	Allocated Regimen	
	OVERALL	
	Any Metformin	
	Yes	No
Compliance		
Yes	70	106

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N = number of patients randomised, n = number of observations

*This table is just a compleness check and its outcome did not affect the ITT, safety or the PP population

#Compliance is explained in table 3.2.2 of this report and in the SAP

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Section 4. Secondary Outcome - All Patients

4.1.1.1.1.1 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Delivery Method (n(%))	Missing	0	1	1
	Spontaneous vaginal delivery	64 (54.2)	65 (60.2)	129 (57.1)
	LSCS in labour	18 (15.3)	14 (13.0)	32 (14.2)
	LSCS pre labour	25 (21.2)	17 (15.7)	42 (18.6)
	Forceps/ventouse	11 (9.3)	12 (11.1)	23 (10.2)
C-SECTION index pregnancy (n(%))	Missing	0	1	1
	Yes	43 (36.4)	31 (28.7)	74 (32.7)
	No	75 (63.6)	77 (71.3)	152 (67.3)
Primary C-SECTION in index pregancy (n(%))	Missing	0	1	1
	Yes	25 (21.2)	22 (20.4)	47 (20.8)
	No	93 (78.8)	86 (79.6)	179 (79.2)

Section 4. Secondary Outcome - All Patients

4.1.1.1.1.2 Birth Outcome - C-SECTION current pregnancy - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency

Table of CSECTIONYN by AllocatedTreatment

CSECTIONYN(C-section coded (Y/N))	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
Missing	1	0	.
Yes	31	43	74
No	77	75	152
Total	108	118	226

Frequency Missing = 1

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
c_section_pp	AllocatedTreatment METFORMIN vs PLACEBO	0.702	0.401	1.230	0.2165	0.2566

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*Analised using logistic regression (binary logit), probability modeled is csec='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_1_1_c_section.lst'

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Section 4. Secondary Outcome - All Patients

4.1.1.1.1.3 Birth Outcome - First ever C-SECTION - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of first_c_section by AllocatedTreatment*

first_c_section(First ever c-section in current pregnancy (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Missing	1	0	.
Yes	22	25	47
No	86	93	179
Total	108	118	226

Frequency Missing = 1

Parameter(s)	*Studied effects*		*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
first_csec_pp	AllocatedTreatment	METFORMIN vs PLACEBO	0.952	0.500	1.811	0.8800	1.0000

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47

*Analised using logistic regression (binary logit), probability modeled is first_csec='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_1_1_c_section.lst'

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Section 4. Secondary Outcome - All Patients

4.1.1.1.2.1 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Delivery Blood Loss (mL)	Mean	519.2	500.0	510.0
	Median	400.0	400.0	400.0
	SD	407.7	550.8	480.9
	MIN,MAX	100,2000	50,5000	50,5000
	Q1,Q3	250,600	250,600	250,600
	n	114	106	220
	Nmiss	4	3	7
Hemorrhage* (n(%))	Missing	4	3	7
	Yes	13 (11.4)	9 (8.5)	22 (10.0)
	No	101 (88.6)	97 (91.5)	198 (90.0)
SAE recorded due to Hemorrhage# (n(%))	Missing	0	1	1
	Yes	5	4	9
	No	8	4	12

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N = number of patients randomised, n = number of observations

*Hemorrhage defined as a blood loss greater than 1000ml

#Only summarised for patients with hemorrhage=yes in the item right above

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Section 4. Secondary Outcome - All Patients

4.1.1.1.2.2 Birth Outcome - Hemorrhage - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency

Table of HEMORRHAGE by AllocatedTreatment

HEMORRHAGE(Heamorrhage (Y/N))	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
Missing	3	4	.
Yes	9	13	22
No	97	101	198
Total	106	114	220

Frequency Missing = 7

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
HEMORRHAGE_pp	AllocatedTreatment METFORMIN vs PLACEBO	0.721	0.295	1.763	0.4732	0.5079

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*Analised using logistic regression (binary logit), probability modeled is Hemorr='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_1_1_postpartum_hemorrhage_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 4. Secondary Outcome - All Patients

4.1.1.1.3 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Parameter(s)	*Categories*	*---------Allocated_Intervention---------* *Placebo N=118*	*Metformin N=109*	*Overall N=227*
Labour Type (n(%))	Missing	0	1	1
	Spontaneous	45 (38.1)	44 (40.7)	89 (39.4)
	Induced	51 (43.2)	47 (43.5)	98 (43.4)
	C-section	22 (18.6)	17 (15.7)	39 (17.3)
Non Spontaneous Reason* (n(%))	Missing	0	1	1
	Post dates	15 (20.5)	8 (12.5)	23 (16.8)
	Pre-eclampsia	3 (4.1)	2 (3.1)	5 (3.6)
	Abruption	0	1 (1.6)	1 (0.7)
	Other maternal condition	21 (28.8)	28 (43.8)	49 (35.8)
	Previous C-section	14 (19.2)	4 (6.3)	18 (13.1)
	Previous obstetric history (other)	3 (4.1)	2 (3.1)	5 (3.6)
	Maternal request	5 (6.8)	3 (4.7)	8 (5.8)
	Suspected fetal compromise	4 (5.5)	8 (12.5)	12 (8.8)
	Malpresentation	3 (4.1)	4 (6.3)	7 (5.1)
	Suspected IUGR	3 (4.1)	0	3 (2.2)
	Suspected Macrosomia	2 (2.7)	4 (6.3)	6 (4.4)

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N = number of patients randomised, n = number of observations

*Only recorded for induced and c-section above

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Section 4. Secondary Outcome - All Patients

4.1.1.1.4 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Gesta_coded by method* (n(%))	Missing	0	1	1
	Sponta_vaginal_delivery_<=37 WEEKS	1 (0.8)	2 (1.9)	3 (1.3)
	Sponta_vaginal_delivery_>37 WEEKS	62 (52.5)	63 (58.3)	125 (55.3)
	LSCS in labour_<=37 WEEKS	1 (0.8)	1 (0.9)	2 (0.9)
	LSCS in labour_>37 WEEKS	17 (14.4)	13 (12.0)	30 (13.3)
	LSCS pre labour_<=37 WEEKS	2 (1.7)	4 (3.7)	6 (2.7)
	LSCS pre labour_>37 WEEKS	23 (19.5)	13 (12.0)	36 (15.9)
	Forceps/ventouse_<=37 WEEKS	0	1 (0.9)	1 (0.4)
	Forceps/ventouse_>37 WEEKS	11 (9.3)	11 (10.2)	22 (9.7)
	TOP_Stillbirth_Miscarriage	1 (0.8)	0	1 (0.4)

N = number of patients randomised, n = number of observations

*This variable is a cross between 'Delivery Method' and 'Baby Gestational age coded'

Section 4. Secondary Outcome - All Patients

4.1.1.1.5 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Gesta_coded by labour* (n(%))	Missing	0	1	1
	Spontaneous_<=37 WEEKS	1 (0.8)	1 (0.9)	2 (0.9)
	Spontaneous_>37 WEEKS	44 (37.3)	43 (39.8)	87 (38.5)
	Induced_<=37 WEEKS	2 (1.7)	3 (2.8)	5 (2.2)
	Induced_>37 WEEKS	48 (40.7)	44 (40.7)	92 (40.7)
	C-section_<=37 WEEKS	1 (0.8)	4 (3.7)	5 (2.2)
	C-section_>37 WEEKS	21 (17.8)	13 (12.0)	34 (15.0)
	TOP_Stillbirth_Miscarriage	1 (0.8)	0	1 (0.4)

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N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Baby Gestational age coded'

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Section 4. Secondary Outcome - All Patients

4.1.1.1.6 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour by method* <=37 Weeks (n(%))	Spontaneous_vaginal_deliv	1 (20.0)	1 (12.5)	2 (15.4)
	Induced_vaginal_deliv	0	1 (12.5)	1 (7.7)
	Induced_LSCS in labour	1 (20.0)	1 (12.5)	2 (15.4)
	Induced_LSCS pre labour	1 (20.0)	0	1 (7.7)
	Induced_Forceps/ventouse	0	1 (12.5)	1 (7.7)
	C-section_LSCS pre labour	1 (20.0)	4 (50.0)	5 (38.5)
	TOP_Stillbirth_Miscarriage	1 (20.0)	0	1 (7.7)

N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Delivery Method' split by 'Baby Gestational age coded'

Section 4. Secondary Outcome - All Patients

4.1.1.1.7 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour by method* >37 Weeks (n(%))	Spontaneous_vaginal_deliv	34 (30.1)	33 (33.0)	67 (31.5)
	Spontaneous_LSCS in labour	3 (2.7)	3 (3.0)	6 (2.8)
	Spontaneous_Forceps/ventouse	7 (6.2)	7 (7.0)	14 (6.6)
	Induced_vaginal_deliv	28 (24.8)	30 (30.0)	58 (27.2)
	Induced_LSCS in labour	14 (12.4)	10 (10.0)	24 (11.3)
	Induced_LSCS pre labour	2 (1.8)	0	2 (0.9)
	Induced_Forceps/ventouse	4 (3.5)	4 (4.0)	8 (3.8)
	C-section_LSCS pre labour	21 (18.6)	13 (13.0)	34 (16.0)

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N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Delivery Method' split by 'Baby Gestational age coded'

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Section 4. Secondary Outcome - All Patients

4.1.1.2.1.1 Delivery Outcome

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Gestational age (Days)*	Mean	276.6	276.6	276.6
	Median	277.5	278.0	278.0
	SD	17.1	11.5	14.7
	MIN,MAX	152,297	219,297	152,297
	Q1,Q3	271,287	271,284	271,285
	n	118	108	226
	Nmiss	0	1	1
Baby Gestational age coded (n(%))*	Missing	0	1	1
	<= 24 WEEKS	1 (0.8)	0	1 (0.4)
	>24 and <=37 WEEKS	4 (3.4)	8 (7.4)	12 (5.3)
	>37 WEEKS	113 (95.8)	100 (92.6)	213 (94.2)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This is repeated from table 3.1 (Recorded Gestation - Visit 8 and Coded R_gestation - Visit 8)

Section 4. Secondary Outcome - All Patients

4.1.1.2.1.1 Delivery Outcome (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Gender (n(%))	NA	0	1	1
	Male	58 (49.2)	54 (50.0)	112 (49.6)
	Female	60 (50.8)	54 (50.0)	114 (50.4)
Birth Outcome (n(%))	NA	0	1	1
	Live Birth	117 (99.2)	108 (100)	225 (99.6)
	Termination of Pregnancy	1 (0.8)	0	1 (0.4)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - All Patients

4.1.1.2.1.2 Birth Outcome - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Birth_Out_Ana by AllocatedTreatment*

Birth_Out_Ana(Birth Outcome categorised for analysis)	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
NA	1	0	.
Live Birth	108	117	225
TOP_Stillbirth_Miscarriage	0	1	1
Total	108	118	226

Frequency Missing = 1

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
BirthOut_pp	AllocatedTreatment METFORMIN vs PLACEBO	<0.001	<0.001	>999.999	0.9604	1.0000

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*Analised using logistic regression (binary logit), probability modeled is Birth_Out_Ana='TOP_Stillbirth_Miscarriage'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_1_2_1_birth_outcome_analysis.lst'

Section 4. Secondary Outcome - All Patients

4.1.1.2.2.1 Delivery Outcome - birth weight

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Birth weight (g)	Mean	3512.4	3503.6	3508.2
	Median	3570.0	3525.0	3550.0
	SD	622.7	562.8	593.5
	MIN,MAX	400,4800	1800,4900	400,4900
	Q1,Q3	3190,3860	3110,3838	3140,3850
	n	118	108	226
	Nmiss	0	1	1

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - All Patients

4.1.1.2.2.2 Delivery Outcome - birth weight split by gender

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight Males (g)	Mean	3603.5	3568.3	3586.5
	Median	3670.0	3540.0	3590.0
	SD	642.1	571.0	606.4
	MIN,MAX	400,4800	2330,4900	400,4900
	Q1,Q3	3308,3970	3135,3880	3273,3908
	n	58	54	112
	Nmiss	0	0	0
Birth weight Females(g)	Mean	3424.3	3438.9	3431.2
	Median	3450.0	3515.0	3485.0
	SD	595.4	552.2	572.9
	MIN,MAX	690,4550	1800,4530	690,4550
	Q1,Q3	3090,3728	3110,3780	3110,3760
	n	60	54	114
	Nmiss	0	0	0

Section 4. Secondary Outcome - All Patients

4.1.1.2.2.3 Delivery Outcome - birth weight split by gestation

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight <=24 WEEKS (g)	Mean		400.0	400.0
	Median		400.0	400.0
	SD		.	.
	MIN,MAX		400,400	400,400
	Q1,Q3		400,400	400,400
	n		1	1
	Nmiss		0	0
Birth weight >24 and <=37 WEEKS (g)	Mean	2721.3	2823.1	2789.2
	Median	2697.5	2737.5	2737.5
	SD	1695.6	629.9	1019.4
	MIN,MAX	690,4800	1800,3740	690,4800
	Q1,Q3	1545,3898	2465,3320	2365,3320
	n	4	8	12
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - All Patients

4.1.1.2.2.3 Delivery Outcome - birth weight split by gestation (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight >37 WEEKS (g)	Mean	3567.9	3558.1	3563.3
	Median	3580.0	3550.0	3570.0
	SD	464.8	523.3	492.0
	MIN,MAX	2600,4700	2110,4900	2110,4900
	Q1,Q3	3240,3860	3200,3890	3220,3860
	n	113	100	213
	Nmiss	0	0	0

Section 4. Secondary Outcome - All Patients

4.1.1.2.2.4 Delivery Outcome - birth weight split by parity

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight parity=0 (g)	Mean	3361.0	3471.7	3421.5
	Median	3380.0	3480.0	3410.0
	SD	597.7	580.8	588.1
	MIN,MAX	690,4450	1800,4900	690,4900
	Q1,Q3	3054,3710	3110,3836	3060,3730
	n	44	53	97
	Nmiss	0	1	1
Birth weight parity=>1 (g)	Mean	3602.4	3534.4	3573.4
	Median	3665.0	3580.0	3640.0
	SD	623.7	548.5	591.5
	MIN,MAX	400,4800	2110,4790	400,4800
	Q1,Q3	3260,3920	3110,3840	3240,3905
	n	74	55	129
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - All Patients

4.1.1.3 Delivery Outcome - Low birth weights

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*Gestation (days) at delivery*	*Delivery date*	*LabourType*	*Birth Outcome categorised as per CRF*	*Baby death date*	*Baby gender*	*Birth weight corrected from kg to g (g)*
21119	PLACEBO	152	10JAN2014	Induced	Termination of Pregnancy	10JAN2014	Male	400
14264	PLACEBO	191	12JAN2013	C-section	Live Birth	.	Female	690
11881	METFORMIN	219	04JAN2014	C-section	Live Birth	.	Female	1800

Section 4. Secondary Outcome - All Patients

4.1.1.4 Delivery Outcome - births before 24 weeks

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Gestation (days) at delivery	Delivery date	LabourType	Birth Outcome categorised as per CRF	Baby death date	Baby gender
21119	PLACEBO	152	10JAN2014	Induced	Termination of Pregnancy	10JAN2014	Male

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.1 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Delivery Method(n(%))	Spontaneous vaginal delivery	63 (53.8)	65 (60.2)	128 (56.9)
	LSCS in labour	18 (15.4)	14 (13.0)	32 (14.2)
	LSCS pre labour	25 (21.4)	17 (15.7)	42 (18.7)
	Forceps/ventouse	11 (9.4)	12 (11.1)	23 (10.2)
C-SECTION index pregnancy(n(%))	Yes	43 (36.8)	31 (28.7)	74 (32.9)
	No	74 (63.2)	77 (71.3)	151 (67.1)
Primary C-SECTION in index pregancy(n(%))	Yes	25 (21.4)	22 (20.4)	47 (20.9)
	No	92 (78.6)	86 (79.6)	178 (79.1)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This is a combination between any c-section on previous pregnancies and current pregnancy c-section

Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.2 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Delivery Blood Loss (mL)	Mean	522.9	500.0	511.8
	Median	400.0	400.0	400.0
	SD	407.6	550.8	481.2
	MIN,MAX	100,2000	50,5000	50,5000
	Q1,Q3	250,600	250,600	250,600
	n	113	106	219
	Nmiss	4	2	6
Hemorrhage* (n(%))	Missing	4	2	6
	Yes	13 (11.5)	9 (8.5)	22 (10.0)
	No	100 (88.5)	97 (91.5)	197 (90.0)
SAE recorded due to Hemorrhage# (n(%))	Missing	0	1	1
	Yes	5	4	9
	No	8	4	12

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N = number of patients randomised, n = number of observations

*Hemorrhage defined as a blood loss greater than 1000ml

#Only summarised for patients with hemorrhage=yes in the item right above

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.3 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour Type (n(%))	Spontaneous	45 (38.5)	44 (40.7)	89 (39.6)
	Induced	50 (42.7)	47 (43.5)	97 (43.1)
	C-section	22 (18.8)	17 (15.7)	39 (17.3)
Non Spontaneous Reason* (n(%))	Post dates	15 (20.8)	8 (12.5)	23 (16.9)
	Pre-eclampsia	3 (4.2)	2 (3.1)	5 (3.7)
	Abruption	0	1 (1.6)	1 (0.7)
	Other maternal condition	21 (29.2)	28 (43.8)	49 (36.0)
	Previous C-section	14 (19.4)	4 (6.3)	18 (13.2)
	Previous obstetric history (other)	3 (4.2)	2 (3.1)	5 (3.7)
	Maternal request	5 (6.9)	3 (4.7)	8 (5.9)
	Suspected fetal compromise	3 (4.2)	8 (12.5)	11 (8.1)
	Malpresentation	3 (4.2)	4 (6.3)	7 (5.1)
	Suspected IUGR	3 (4.2)	0	3 (2.2)
	Suspected Macrosomia	2 (2.8)	4 (6.3)	6 (4.4)

N = number of patients randomised, n = number of observations

*Only recorded for induced and c-section above

Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.4.1 Delivery Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Gesta_coded by method* (n(%))	Sponta_vaginal_delivery_<=37 WEEKS	1 (0.9)	2 (1.9)	3 (1.3)
	Sponta_vaginal_delivery_>37 WEEKS	62 (53.0)	63 (58.3)	125 (55.6)
	LSCS in labour_<=37 WEEKS	1 (0.9)	1 (0.9)	2 (0.9)
	LSCS in labour_>37 WEEKS	17 (14.5)	13 (12.0)	30 (13.3)
	LSCS pre labour_<=37 WEEKS	2 (1.7)	4 (3.7)	6 (2.7)
	LSCS pre labour_>37 WEEKS	23 (19.7)	13 (12.0)	36 (16.0)
	Forceps/ventouse_<=37 WEEKS	0	1 (0.9)	1 (0.4)
	Forceps/ventouse_>37 WEEKS	11 (9.4)	11 (10.2)	22 (9.8)
Gesta_coded by labour# (n(%))	Spontaneous_<=37 WEEKS	1 (0.9)	1 (0.9)	2 (0.9)
	Spontaneous_>37 WEEKS	44 (37.6)	43 (39.8)	87 (38.7)
	Induced_<=37 WEEKS	2 (1.7)	3 (2.8)	5 (2.2)
	Induced_>37 WEEKS	48 (41.0)	44 (40.7)	92 (40.9)
	C-section_<=37 WEEKS	1 (0.9)	4 (3.7)	5 (2.2)
	C-section_>37 WEEKS	21 (17.9)	13 (12.0)	34 (15.1)

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N = number of patients randomised, n = number of observations
*This variable is a cross between 'Delivery Method' and 'Baby Gestational age coded'
#This variable is a cross between 'Labour Type' and 'Baby Gestational age coded'

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.4.2 Delivery Details (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Labour by method* <=37 Weeks (n(%))	Spontaneous_vaginal_deliv	1 (25.0)	1 (12.5)	2 (16.7)
	Induced_vaginal_deliv	0	1 (12.5)	1 (8.3)
	Induced_LSCS in labour	1 (25.0)	1 (12.5)	2 (16.7)
	Induced_LSCS pre labour	1 (25.0)	0	1 (8.3)
	Induced_Forceps/ventouse	0	1 (12.5)	1 (8.3)
	C-section_LSCS pre labour	1 (25.0)	4 (50.0)	5 (41.7)
Labour by method* >37 Weeks (n(%))	Spontaneous_vaginal_deliv	34 (30.1)	33 (33.0)	67 (31.5)
	Spontaneous_LSCS in labour	3 (2.7)	3 (3.0)	6 (2.8)
	Spontaneous_Forceps/ventouse	7 (6.2)	7 (7.0)	14 (6.6)
	Induced_vaginal_deliv	28 (24.8)	30 (30.0)	58 (27.2)
	Induced_LSCS in labour	14 (12.4)	10 (10.0)	24 (11.3)
	Induced_LSCS pre labour	2 (1.8)	0	2 (0.9)
	Induced_Forceps/ventouse	4 (3.5)	4 (4.0)	8 (3.8)
	C-section_LSCS pre labour	21 (18.6)	13 (13.0)	34 (16.0)

N = number of patients randomised, n = number of observations

*This variable is a cross between 'Labour Type' and 'Delivery Method' split by 'Baby Gestational age coded'

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.1.4.3 Delivery Details - Preterm Birth - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of GESTA_2CODE by AllocatedTreatment*

GESTA_2CODE(Gestation Code 2)	AllocatedTreatment(Allocated Treatment) METFORMIN	PLACEBO	Total
>24 and <=37 WEEKS	8	4	12
>37 WEEKS	100	113	213
Total	108	117	225

Parameter(s)	Studied effects	Odds Ratio Estimate	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio	P-value#	Fisher exact P-value#
PRETERM_pp	AllocatedTreatment METFORMIN vs PLACEBO	2.260	0.661	7.732	0.1939	0.2392

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*Analised using logistic regression (binary logit), probability modeled is PRETERM='>24 and <=37 Weeks'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_1_2_1_preterm_birth.lst'

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.1.1 Delivery Outcome

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth Outcome (n(%))	Live Birth	117 (100)	108 (100)	225 (100)
Baby Gender (n(%))	Male	57 (48.7)	54 (50.0)	111 (49.3)
	Female	60 (51.3)	54 (50.0)	114 (50.7)

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.1.2 Delivery Outcome - Birth Outcome-Neonatal Death after delivery - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency

Table of BirthOutcome by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
BirthOutcome(Birth Outcome categorised as per CRF)	*METFORMIN*	*PLACEBO*	*Total*
Live Birth	108	117	225
Total	108	117	225

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
NEO_DEATH_pp	AllocatedTreatment METFORMIN vs PLACEBO	<0.001	<0.001	>999.999	0.9603	1.0000

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*Analised using logistic regression (binary logit), probability modeled is BirthOutcome='Live Birth-followed by neonatal death'

#Significance level set at p<0.05

Fisher's exact test should be used for reporting due to low cell count

Detailed analysis in file 'Empowar_11_2_Neonatal_unit.lst'

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.1.3 Delivery Outcome(Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Baby Gestational age (Days)*	Mean	277.6	276.6	277.1
	Median	278.0	278.0	278.0
	SD	12.7	11.5	12.1
	MIN,MAX	191,297	219,297	191,297
	Q1,Q3	271,287	271,284	271,285
	n	117	108	225
	Nmiss	0	0	0
Baby Gestational age coded (n(%))*	>24 and <=37 WEEKS	4 (3.4)	8 (7.4)	12 (5.3)
	>37 WEEKS	113 (96.6)	100 (92.6)	213 (94.7)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This is repeated from table 3.1 (Recorded Gestation - Visit 8 and Coded R_gestation - Visit 8)

Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.1 Delivery Outcome - birth weight

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight (g)	Mean	3539.0	3503.6	3522.0
	Median	3570.0	3525.0	3550.0
	SD	553.9	562.8	557.2
	MIN,MAX	690,4800	1800,4900	690,4900
	Q1,Q3	3200,3860	3110,3838	3150,3850
	n	117	108	225
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.2 Delivery Outcome - birth weight split by gender

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight Males (g)	Mean	3659.7	3568.3	3615.2
	Median	3670.0	3540.0	3600.0
	SD	482.9	571.0	527.1
	MIN,MAX	2720,4800	2330,4900	2330,4900
	Q1,Q3	3310,3970	3135,3880	3285,3910
	n	57	54	111
	Nmiss	0	0	0
Birth weight Females(g)	Mean	3424.3	3438.9	3431.2
	Median	3450.0	3515.0	3485.0
	SD	595.4	552.2	572.9
	MIN,MAX	690,4550	1800,4530	690,4550
	Q1,Q3	3090,3728	3110,3780	3110,3760
	n	60	54	114
	Nmiss	0	0	0

Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.3 Delivery Outcome - birth weight split by gestation

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight >24 and <=37 WEEKS (g)	Mean	2721.3	2823.1	2789.2
	Median	2697.5	2737.5	2737.5
	SD	1695.6	629.9	1019.4
	MIN,MAX	690,4800	1800,3740	690,4800
	Q1,Q3	1545,3898	2465,3320	2365,3320
	n	4	8	12
	Nmiss	0	0	0
Birth weight >37 WEEKS (g)	Mean	3567.9	3558.1	3563.3
	Median	3580.0	3550.0	3570.0
	SD	464.8	523.3	492.0
	MIN,MAX	2600,4700	2110,4900	2110,4900
	Q1,Q3	3240,3860	3200,3890	3220,3860
	n	113	100	213
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 4. Secondary Outcome - Only Alive Births

4.1.2.2.2.4 Delivery Outcome - birth weight split by parity

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight parity=0 (g)	Mean	3361.0	3471.7	3421.5
	Median	3380.0	3480.0	3410.0
	SD	597.7	580.8	588.1
	MIN,MAX	690,4450	1800,4900	690,4900
	Q1,Q3	3054,3710	3110,3836	3060,3730
	n	44	53	97
	Nmiss	0	0	0
Birth weight parity=>1 (g)	Mean	3646.2	3534.4	3598.2
	Median	3670.0	3580.0	3645.0
	SD	500.0	548.5	522.2
	MIN,MAX	2600,4800	2110,4790	2110,4800
	Q1,Q3	3290,3920	3110,3840	3240,3908
	n	73	55	128
	Nmiss	0	0	0

Section 4. Secondary Outcome - Only Alive Births

4.1.2.3 Delivery Outcome - Low birth weights

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Gestation (days) at delivery	Delivery date	LabourType	Birth Outcome categorised as per CRF	Baby death date	Baby gender	Birth weight corrected from kg to g (g)
14264	PLACEBO	191	12JAN2013	C-section	Live Birth	.	Female	690
11881	METFORMIN	219	04JAN2014	C-section	Live Birth	.	Female	1800

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DOI: 10.3310/eme03070

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Section 4. Outcomes - Only Alive Births

4.2.1.1 PRIMARY EFFICACY: Birth weight centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile	Mean	58.527	59.894	59.183
	Median	59.685	64.530	63.585
	SD	27.690	28.273	27.917
	MIN,MAX	1.58,99.95	0.03,99.83	0.03,99.95
	Q1,Q3	34.33,82.48	34.95,83.13	34.53,82.77
	n	117	108	225
	Nmiss	0	0	0

Section 4. Outcomes - Only Alive Births

4.2.1.2 PRIMARY EFFICACY: Birth weight centile split by gender

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile Males	Mean	59.594	57.029	58.346
	Median	62.022	62.261	62.022
	SD	27.780	28.811	28.186
	MIN,MAX	1.58,99.95	3.91,99.76	1.58,99.95
	Q1,Q3	35.73,82.48	33.65,79.74	33.69,79.89
	n	57	54	111
	Nmiss	0	0	0
Birth weight centile Females	Mean	57.513	62.759	59.998
	Median	57.154	66.501	64.268
	SD	27.800	27.695	27.752
	MIN,MAX	3.75,99.34	0.03,99.83	0.03,99.83
	Q1,Q3	34.31,82.72	38.90,87.36	35.35,86.16
	n	60	54	114
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Outcomes - Only Alive Births

4.2.1.3 PRIMARY EFFICACY: Birth weight centile split by gestation

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile >24 and <=37 WEEKS	Mean	55.075	70.181	65.146
	Median	50.782	80.241	76.141
	SD	37.927	28.695	31.171
	MIN,MAX	18.78,99.95	20.03,97.13	18.78,99.95
	Q1,Q3	23.90,86.25	50.45,91.45	31.14,91.45
	n	4	8	12
	Nmiss	0	0	0
Birth weight centile >37 WEEKS (g)	Mean	58.649	59.071	58.847
	Median	59.685	63.906	62.996
	SD	27.480	28.222	27.766
	MIN,MAX	1.58,99.34	0.03,99.83	0.03,99.83
	Q1,Q3	35.17,82.48	34.95,82.77	35.17,82.60
	n	113	100	213
	Nmiss	0	0	0

Section 4. Outcomes - Only Alive Births

4.2.1.4 PRIMARY EFFICACY: Birth weight centile split by parity

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile parity=0 (g)	Mean	54.041	59.862	57.222
	Median	50.234	66.310	56.322
	SD	27.729	29.505	28.713
	MIN,MAX	3.34,97.52	3.91,99.83	3.34,99.83
	Q1,Q3	30.56,78.50	33.69,84.14	32.13,83.49
	n	44	53	97
	Nmiss	0	0	0
Birth weight centile parity=>1 (g)	Mean	61.230	59.924	60.669
	Median	65.879	64.228	64.490
	SD	27.502	27.306	27.318
	MIN,MAX	1.58,99.95	0.03,99.28	0.03,99.95
	Q1,Q3	39.95,82.60	38.37,82.77	39.10,82.69
	n	73	55	128
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 4. Outcomes - Only Alive Births

4.2.2.1.1 PRIMARY EFFICACY: Birth weight centile categorised

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile (n(%))	<=3rd	1 (0.9)	1 (0.9)	2 (0.9)
	>3rd and <=5th	2 (1.7)	2 (1.9)	4 (1.8)
	>5th and <=10th	3 (2.6)	3 (2.8)	6 (2.7)
	>10th and <=90th	90 (76.9)	81 (75.0)	171 (76.0)
	>90th and <=95th	9 (7.7)	9 (8.3)	18 (8.0)
	>95th and <=97th	5 (4.3)	4 (3.7)	9 (4.0)
	>97th	7 (6.0)	8 (7.4)	15 (6.7)

Section 4. Secondary Outcome - Only Alive Births

4.2.2.1.2 PRIMARY EFFICACY: Birth weight centile categorised - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of centile_03b by AllocatedTreatment*

	AllocatedTreatment(Allocated Treatment)		
centile_03b	*METFORMIN*	*PLACEBO*	*Total*
No	107	116	223
Yes	1	1	2
Total	108	117	225

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
centile_03b_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.084	0.067	17.549	0.9547	1.0000

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*Analised using logistic regression (binary logit), probability modeled is centile_03b='Yes'

#Significance level set at p<0.05

Fisher's exact test should be used for reporting due to low cell count

Detailed analysis in file 'Empowar_4_2_2_1_weight_centile.lst'

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DOI: 10.3310/eme03070

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Section 4. Secondary Outcome - Only Alive Births

4.2.2.1.3 PRIMARY EFFICACY: Birth weight centile categorised - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of centile_10b by AllocatedTreatment*

	AllocatedTreatment(Allocated Treatment)		
centile_10b	*METFORMIN*	*PLACEBO*	*Total*
No	102	111	213
Yes	6	6	12
Total	108	117	225

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
centile_10b_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.088	0.340	3.482	0.8867	1.0000

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*Analised using logistic regression (binary logit), probability modeled is centile_10b='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_4_2_2_1_weight_centile.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 4. Outcomes - Only Alive Births

4.2.2.2 PRIMARY EFFICACY: Birth weight centile categorised split by gender

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile Males(n(%))	<=3rd	1 (1.8)	0	1 (0.9)
	>3rd and <=5th	1 (1.8)	2 (3.7)	3 (2.7)
	>5th and <=10th	2 (3.5)	2 (3.7)	4 (3.6)
	>10th and <=90th	42 (73.7)	41 (75.9)	83 (74.8)
	>90th and <=95th	5 (8.8)	2 (3.7)	7 (6.3)
	>95th and <=97th	3 (5.3)	3 (5.6)	6 (5.4)
	>97th	3 (5.3)	4 (7.4)	7 (6.3)
Split Birth weight Centile Females(n(%))	<=3rd	0	1 (1.9)	1 (0.9)
	>3rd and <=5th	1 (1.7)	0	1 (0.9)
	>5th and <=10th	1 (1.7)	1 (1.9)	2 (1.8)
	>10th and <=90th	48 (80.0)	40 (74.1)	88 (77.2)
	>90th and <=95th	4 (6.7)	7 (13.0)	11 (9.6)
	>95th and <=97th	2 (3.3)	1 (1.9)	3 (2.6)
	>97th	4 (6.7)	4 (7.4)	8 (7.0)

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Section 4. Outcomes - Only Alive Births

4.2.2.3 PRIMARY EFFICACY: Birth weight centile categorised split by gestation

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile >24 and <=37 WEEKS(n(%))	>10th and <=90th	3 (75.0)	6 (75.0)	9 (75.0)
	>95th and <=97th	0	1 (12.5)	1 (8.3)
	>97th	1 (25.0)	1 (12.5)	2 (16.7)
Split Birth weight Centile >37 WEEKS(n(%))	<=3rd	1 (0.9)	1 (1.0)	2 (0.9)
	>3rd and <=5th	2 (1.8)	2 (2.0)	4 (1.9)
	>5th and <=10th	3 (2.7)	3 (3.0)	6 (2.8)
	>10th and <=90th	87 (77.0)	75 (75.0)	162 (76.1)
	>90th and <=95th	9 (8.0)	9 (9.0)	18 (8.5)
	>95th and <=97th	5 (4.4)	3 (3.0)	8 (3.8)
	>97th	6 (5.3)	7 (7.0)	13 (6.1)

Section 4. Outcomes - Only Alive Births

4.2.2.4 PRIMARY EFFICACY: Birth weight centile categorised split by parity

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Split Birth weight Centile parity=0 (n(%))	>3rd and <=5th	1 (2.3)	2 (3.8)	3 (3.1)
	>5th and <=10th	1 (2.3)	1 (1.9)	2 (2.1)
	>10th and <=90th	37 (84.1)	39 (73.6)	76 (78.4)
	>90th and <=95th	1 (2.3)	6 (11.3)	7 (7.2)
	>95th and <=97th	3 (6.8)	0	3 (3.1)
	>97th	1 (2.3)	5 (9.4)	6 (6.2)
Split Birth weight Centile parity=>1 (n(%))	<=3rd	1 (1.4)	1 (1.8)	2 (1.6)
	>3rd and <=5th	1 (1.4)	0	1 (0.8)
	>5th and <=10th	2 (2.7)	2 (3.6)	4 (3.1)
	>10th and <=90th	53 (72.6)	42 (76.4)	95 (74.2)
	>90th and <=95th	8 (11.0)	3 (5.5)	11 (8.6)
	>95th and <=97th	2 (2.7)	4 (7.3)	6 (4.7)
	>97th	6 (8.2)	3 (5.5)	9 (7.0)

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Section 4. Outcomes - Only Alive Births

4.3.1 PRIMARY EFFICACY: Calculated Z score

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Z-score for birth weight centile	Mean	0.3130	0.3604	0.3358
	Median	0.2452	0.3727	0.3474
	SD	0.9781	1.0580	1.0152
	MIN,MAX	-2.150,3.299	-3.428,2.929	-3.428,3.299
	Q1,Q3	-0.404,0.934	-0.387,0.959	-0.398,0.945
	n	117	108	225
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 4. Outcomes - Only Alive Births

4.3.2 PRIMARY EFFICACY: Calculated Z score - Statistical Analysis

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
z-score - pp	0.270	0.1584	117	0.338	0.1506	108	0.068	-0.188	0.324	0.276	0.6001

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 4.3.1 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means for the z score by allocated treatment,
SE represents standard error of the estimated mean and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_4_3_2_primary_outcome_z_analysis.lst'
Parameter shown normal behavior

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.1 Fasted Glucose - Visit 3 Randomisation (12-16 Weeks)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
GTT - V3 - base (mmol/L)	Mean	4.42	4.41	4.41
	Median	4.40	4.40	4.40
	SD	0.36	0.37	0.36
	MIN,MAX	3.5,5.6	3.5,5.4	3.5,5.6
	Q1,Q3	4.2,4.6	4.1,4.7	4.1,4.7
	n	118	109	227
	Nmiss	0	0	0
GTT - V3 - 2 hr (mmol/L)	Mean	5.45	5.17	5.31
	Median	5.45	5.10	5.30
	SD	1.18	1.10	1.15
	MIN,MAX	2.6,7.8	2.2,7.7	2.2,7.8
	Q1,Q3	4.6,6.4	4.6,5.9	4.6,6.1
	n	118	109	227
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*If baseline (fasting) sample >5.5 mmol/L or 2 hr sample >7.8 mmol then the subject is not eligible to continue in the study

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.2 Fasted Glucose - Visit 5 (28 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
GTT - V5 - base (mmol/L)	Mean	4.49	4.34	4.42
	Median	4.45	4.30	4.40
	SD	0.43	0.38	0.41
	MIN,MAX	3.7,5.6	3.4,5.2	3.4,5.6
	Q1,Q3	4.2,4.8	4.1,4.6	4.2,4.7
	n	116	109	225
	Nmiss	2	0	2
GTT - V5 - 2 hr (mmol/L)	Mean	5.90	5.56	5.74
	Median	5.85	5.50	5.60
	SD	1.18	1.20	1.20
	MIN,MAX	2.4,8.3	3.1,10.0	2.4,10.0
	Q1,Q3	5.1,6.7	4.9,6.1	5.0,6.5
	n	116	108	224
	Nmiss	2	1	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.3 Fasted Glucose - Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
GTT - V6 - base (mmol/L)	Mean	4.43	4.34	4.39
	Median	4.40	4.20	4.30
	SD	0.51	0.45	0.48
	MIN,MAX	2.7,5.8	3.4,5.9	2.7,5.9
	Q1,Q3	4.0,4.8	4.0,4.6	4.0,4.7
	n	104	93	197
	Nmiss	14	16	30
GTT - V6 - 2 hr (mmol/L)	Mean	6.04	5.79	5.92
	Median	5.90	5.70	5.80
	SD	1.53	1.34	1.44
	MIN,MAX	3.0,10.3	2.7,9.1	2.7,10.3
	Q1,Q3	4.9,7.2	5.0,6.5	4.9,6.8
	n	103	92	195
	Nmiss	15	17	32

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.4.1 Fasted Glucose - Visit 6 (36 Weeks) - Statistical Analysis

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Glucose_V6_Baseline - pp	4.458	0.0767	104	4.367	0.0735	93	-0.091	-0.221	0.040	1.875	0.1726
Glucose_V6_Two_Hour - pp	6.052	0.2315	103	5.804	0.2217	92	-0.248	-0.643	0.148	1.529	0.2179

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 5.1.3 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means for the glucose in blood by allocated treatment,
SE represents standard error of the estimated mean and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_1_4_glucose_outcome_analysis.lst'
Parameters shown normal or near-normal behavior

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.4.2 Fasted Glucose - Visit 5 (28 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Glucose_V5_Baseline - pp	4.454	0.0650	116	4.313	0.0613	109	-0.141	-0.246	-0.036	7.044	0.0086
Glucose_V5_Two_Hour - pp	5.766	0.1908	116	5.454	0.1801	108	-0.312	-0.620	-0.004	3.989	0.0471

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 5.1.2 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means for the glucose in blood by allocated treatment,
SE represents standard error of the estimated mean and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_1_4_glucose_outcome_analysis_v5.lst'
Parameters shown normal or near-normal behavior

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.1 Fasted Glucose - Visit 5 (28 Weeks) split by C-section

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - GTT - V5 - base (mmol/L)	Mean	4.58	4.37	4.49
	Median	4.60	4.40	4.50
	SD	0.48	0.37	0.45
	MIN,MAX	3.7,5.5	3.5,5.0	3.5,5.5
	Q1,Q3	4.2,5.0	4.2,4.7	4.2,4.8
	n	43	31	74
	Nmiss	0	0	0
Yes C-section - GTT - V5 - 2 hr (mmol/L)	Mean	6.26	5.90	6.11
	Median	6.30	5.60	6.00
	SD	1.46	1.24	1.37
	MIN,MAX	2.4,8.3	4.2,8.9	2.4,8.9
	Q1,Q3	5.3,7.5	5.1,6.5	5.1,7.3
	n	43	31	74
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.1 Fasted Glucose - Visit 5 (28 Weeks) split by C-section

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
No C-section - GTT - V5 - base (mmol/L)	Mean	4.44	4.33	4.38
	Median	4.40	4.30	4.40
	SD	0.39	0.39	0.39
	MIN,MAX	3.7,5.6	3.4,5.2	3.4,5.6
	Q1,Q3	4.2,4.7	4.1,4.6	4.1,4.6
	n	73	77	150
	Nmiss	2	0	2
No C-section - GTT - V5 - 2 hr (mmol/L)	Mean	5.68	5.44	5.56
	Median	5.60	5.45	5.50
	SD	0.93	1.17	1.06
	MIN,MAX	3.5,8.3	3.1,10.0	3.1,10.0
	Q1,Q3	5.0,6.3	4.8,6.0	4.9,6.2
	n	73	76	149
	Nmiss	2	1	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.2 Fasted Glucose - Visit 6 (36 Weeks) split by C-section

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - GTT - V6 - base (mmol/L)	Mean	4.42	4.34	4.39
	Median	4.50	4.30	4.40
	SD	0.53	0.44	0.49
	MIN,MAX	2.7,5.6	3.6,5.5	2.7,5.6
	Q1,Q3	4.0,4.8	4.0,4.5	4.0,4.7
	n	38	25	63
	Nmiss	5	4	9
Yes C-section - GTT - V6 - 2 hr (mmol/L	Mean	6.32	5.85	6.13
	Median	6.30	5.80	6.10
	SD	1.65	1.20	1.49
	MIN,MAX	3.0,10.3	2.7,8.0	2.7,10.3
	Q1,Q3	5.1,7.4	5.5,6.5	5.2,7.2
	n	38	25	63
	Nmiss	5	4	9

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.2 Fasted Glucose - Visit 6 (36 Weeks) split by C-section

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
No C-section - GTT - V6 - base (mmol/L)	Mean	4.43	4.34	4.38
	Median	4.30	4.20	4.30
	SD	0.50	0.46	0.48
	MIN,MAX	3.4,5.8	3.4,5.9	3.4,5.9
	Q1,Q3	4.1,4.7	4.0,4.6	4.0,4.6
	n	66	68	134
	Nmiss	9	9	18
No C-section - GTT - V6 - 2 hr (mmol/L)	Mean	5.88	5.76	5.82
	Median	5.70	5.70	5.70
	SD	1.44	1.39	1.41
	MIN,MAX	3.5,9.8	3.2,9.1	3.2,9.8
	Q1,Q3	4.9,6.8	4.9,6.4	4.9,6.5
	n	65	67	132
	Nmiss	10	10	20

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_GTT_V5_base (mmol/L)	Mean	4.00	4.00	4.00
	Median	4.00	4.00	4.00
	SD	.	.	0.00
	MIN,MAX	4.0,4.0	4.0,4.0	4.0,4.0
	Q1,Q3	4.0,4.0	4.0,4.0	4.0,4.0
	n	1	1	2
	Nmiss	0	0	0
3%<=_GTT_V5_2 hr (mmol/L)	Mean	4.80	5.10	4.95
	Median	4.80	5.10	4.95
	SD	.	.	0.21
	MIN,MAX	4.8,4.8	5.1,5.1	4.8,5.1
	Q1,Q3	4.8,4.8	5.1,5.1	4.8,5.1
	n	1	1	2
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
5%<=_GTT_V5_base (mmol/L)	Mean	4.03	4.00	4.02
	Median	4.00	4.00	4.00
	SD	0.06	0.40	0.26
	MIN,MAX	4.0,4.1	3.6,4.4	3.6,4.4
	Q1,Q3	4.0,4.1	3.6,4.4	4.0,4.1
	n	3	3	6
	Nmiss	0	0	0
5%<=_GTT_V5_2 hr (mmol/L)	Mean	4.07	4.93	4.50
	Median	4.80	5.10	4.90
	SD	1.45	1.06	1.23
	MIN,MAX	2.4,5.0	3.8,5.9	2.4,5.9
	Q1,Q3	2.4,5.0	3.8,5.9	3.8,5.1
	n	3	3	6
	Nmiss	0	0	0

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_GTT_V5_base (mmol/L)	Mean	4.38	4.15	4.27
	Median	4.25	4.20	4.25
	SD	0.43	0.34	0.39
	MIN,MAX	4.0,5.0	3.6,4.5	3.6,5.0
	Q1,Q3	4.0,4.8	4.0,4.4	4.0,4.5
	n	6	6	12
	Nmiss	0	0	0
10%<=_GTT_V5_2 hr (mmol/L)	Mean	4.63	4.72	4.68
	Median	4.90	4.75	4.90
	SD	1.27	0.89	1.05
	MIN,MAX	2.4,6.2	3.7,5.9	2.4,6.2
	Q1,Q3	4.2,5.2	3.8,5.4	4.0,5.3
	n	6	6	12
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%> AND 90%<=_GTT_V5_base (mmol/L)	Mean	4.47	4.34	4.41
	Median	4.40	4.30	4.40
	SD	0.42	0.40	0.41
	MIN,MAX	3.7,5.5	3.4,5.2	3.4,5.5
	Q1,Q3	4.2,4.7	4.1,4.6	4.2,4.7
	n	89	81	170
	Nmiss	1	0	1
10%> AND 90%<=_GTT_V5_2 hr (mmol/L)	Mean	5.86	5.64	5.76
	Median	5.80	5.60	5.70
	SD	1.13	1.25	1.19
	MIN,MAX	3.5,8.3	3.1,10.0	3.1,10.0
	Q1,Q3	5.1,6.7	4.9,6.4	5.0,6.5
	n	89	80	169
	Nmiss	1	1	2

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_GTT_V5_base (mmol/L)	Mean	4.60	4.41	4.50
	Median	4.70	4.40	4.55
	SD	0.48	0.33	0.42
	MIN,MAX	3.7,5.6	3.7,5.0	3.7,5.6
	Q1,Q3	4.4,4.9	4.3,4.7	4.3,4.7
	n	21	21	42
	Nmiss	0	0	0
90%>_GTT_V5_2 hr (mmol/L)	Mean	6.40	5.58	5.99
	Median	6.30	5.50	5.90
	SD	1.14	1.03	1.15
	MIN,MAX	4.4,8.3	3.6,8.4	3.6,8.4
	Q1,Q3	5.4,7.4	5.1,6.0	5.2,6.9
	n	21	21	42
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
95%>_GTT_V5_base (mmol/L)	Mean	4.60	4.46	4.53
	Median	4.55	4.45	4.55
	SD	0.49	0.25	0.39
	MIN,MAX	4.0,5.6	4.0,4.8	4.0,5.6
	Q1,Q3	4.3,4.9	4.3,4.7	4.3,4.7
	n	12	12	24
	Nmiss	0	0	0
95%>_GTT_V5_2 hr (mmol/L)	Mean	6.30	5.58	5.94
	Median	6.15	5.70	5.95
	SD	0.97	1.21	1.13
	MIN,MAX	5.2,8.3	3.6,8.4	3.6,8.4
	Q1,Q3	5.4,7.0	4.9,6.1	5.3,6.4
	n	12	12	24
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.3 Fasted Glucose - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_GTT_V5_base (mmol/L)	Mean	4.71	4.45	4.57
	Median	4.70	4.45	4.60
	SD	0.48	0.29	0.40
	MIN,MAX	4.1,5.6	4.0,4.8	4.0,5.6
	Q1,Q3	4.4,5.0	4.3,4.7	4.3,4.7
	n	7	8	15
	Nmiss	0	0	0
97%>_GTT_V5_2 hr (mmol/L)	Mean	5.93	5.45	5.67
	Median	5.90	5.95	5.90
	SD	0.71	1.00	0.88
	MIN,MAX	5.2,7.1	3.6,6.3	3.6,7.1
	Q1,Q3	5.3,6.4	4.9,6.1	5.3,6.3
	n	7	8	15
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_GTT_V6_base (mmol/L)	Mean	3.40	.	3.40
	Median	3.40	.	3.40
	SD	.	.	.
	MIN,MAX	3.4,3.4	.,.	3.4,3.4
	Q1,Q3	3.4,3.4	.,.	3.4,3.4
	n	1	0	1
	Nmiss	0	1	1
3%<=_GTT_V6_2 hr (mmol/L)	Mean	7.40	.	7.40
	Median	7.40	.	7.40
	SD	.	.	.
	MIN,MAX	7.4,7.4	.,.	7.4,7.4
	Q1,Q3	7.4,7.4	.,.	7.4,7.4
	n	1	0	1
	Nmiss	0	1	1

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
5%<=_GTT_V6_base (mmol/L)	Mean	3.73	3.90	3.80
	Median	3.90	3.90	3.90
	SD	0.29	0.42	0.31
	MIN,MAX	3.4,3.9	3.6,4.2	3.4,4.2
	Q1,Q3	3.4,3.9	3.6,4.2	3.6,3.9
	n	3	2	5
	Nmiss	0	1	1
5%<=_GTT_V6_2 hr (mmol/L)	Mean	5.30	5.40	5.34
	Median	5.50	5.40	5.50
	SD	2.21	1.13	1.66
	MIN,MAX	3.0,7.4	4.6,6.2	3.0,7.4
	Q1,Q3	3.0,7.4	4.6,6.2	4.6,6.2
	n	3	2	5
	Nmiss	0	1	1

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_GTT_V6_base (mmol/L)	Mean	4.13	4.38	4.25
	Median	4.10	4.60	4.30
	SD	0.49	0.49	0.48
	MIN,MAX	3.4,4.7	3.6,4.8	3.4,4.8
	Q1,Q3	3.9,4.6	4.2,4.7	3.9,4.7
	n	6	5	11
	Nmiss	0	1	1
10%<=_GTT_V6_2 hr (mmol/L)	Mean	5.92	4.92	5.46
	Median	5.85	5.20	5.80
	SD	1.72	1.39	1.59
	MIN,MAX	3.0,7.9	2.7,6.2	2.7,7.9
	Q1,Q3	5.5,7.4	4.6,5.9	4.6,6.2
	n	6	5	11
	Nmiss	0	1	1

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%> AND 90%<=_GTT_V6_base (mmol/L)	Mean	4.41	4.31	4.37
	Median	4.40	4.20	4.30
	SD	0.50	0.46	0.48
	MIN,MAX	2.7,5.8	3.4,5.9	2.7,5.9
	Q1,Q3	4.0,4.7	4.0,4.6	4.0,4.7
	n	80	69	149
	Nmiss	10	11	21
10%> AND 90%<=_GTT_V6_2 hr (mmol/L)	Mean	5.84	5.88	5.86
	Median	5.70	5.70	5.70
	SD	1.46	1.43	1.44
	MIN,MAX	3.2,9.5	3.2,9.1	3.2,9.5
	Q1,Q3	4.6,6.8	4.9,6.5	4.8,6.7
	n	79	69	148
	Nmiss	11	11	22

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_GTT_V6_base (mmol/L)	Mean	4.61	4.41	4.51
	Median	4.40	4.40	4.40
	SD	0.54	0.43	0.49
	MIN,MAX	3.8,5.6	3.9,5.5	3.8,5.6
	Q1,Q3	4.3,5.0	4.1,4.6	4.2,4.8
	n	18	19	37
	Nmiss	3	1	4
90%>_GTT_V6_2 hr (mmol/L)	Mean	6.94	5.67	6.30
	Median	6.80	5.75	6.00
	SD	1.52	0.84	1.37
	MIN,MAX	5.1,10.3	3.6,7.2	3.6,10.3
	Q1,Q3	5.8,7.5	5.0,6.1	5.3,7.1
	n	18	18	36
	Nmiss	3	2	5

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
95%>_GTT_V6_base (mmol/L)	Mean	4.88	4.31	4.58
	Median	4.80	4.30	4.40
	SD	0.53	0.34	0.52
	MIN,MAX	4.2,5.6	3.9,5.1	3.9,5.6
	Q1,Q3	4.4,5.3	4.0,4.4	4.2,5.0
	n	9	10	19
	Nmiss	3	1	4
95%>_GTT_V6_2 hr (mmol/L)	Mean	7.06	5.90	6.48
	Median	7.20	5.90	6.05
	SD	1.40	0.77	1.25
	MIN,MAX	5.1,9.8	5.0,7.2	5.0,9.8
	Q1,Q3	6.1,7.5	5.3,6.0	5.8,7.2
	n	9	9	18
	Nmiss	3	2	5

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.5.4 Fasted Glucose - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_GTT_V6_base (mmol/L)	Mean	5.08	4.31	4.59
	Median	5.15	4.30	4.40
	SD	0.51	0.39	0.56
	MIN,MAX	4.4,5.6	3.9,5.1	3.9,5.6
	Q1,Q3	4.7,5.5	4.0,4.4	4.2,5.1
	n	4	7	11
	Nmiss	3	0	3
97%>_GTT_V6_2 hr (mmol/L)	Mean	7.83	5.88	6.66
	Median	7.85	5.60	6.40
	SD	1.66	0.97	1.56
	MIN,MAX	5.8,9.8	5.0,7.2	5.0,9.8
	Q1,Q3	6.7,9.0	5.0,6.9	5.3,7.5
	n	4	6	10
	Nmiss	3	1	4

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.1 Gestational diabetes mellitus (GDM) - OGTT Test*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
GDM WHO CRITERIA*# (n(%))	Missing	15	16	31
	No	84 (81.6)	80 (86.0)	164 (83.7)
	Yes	19 (18.4)	13 (14.0)	32 (16.3)
GDM WHO CRITERIA CODED# (n(%))	Missing	15	16	31
	GDM first at visit 5 (28 weeks)	8 (7.8)	6 (6.5)	14 (7.1)
	GDM first at visit 6 (36 weeks)	11 (10.7)	7 (7.5)	18 (9.2)
	NO GDM	84 (81.6)	80 (86.0)	164 (83.7)
GDM IADPSG CRITERIA*$ (n(%))	Missing	14	17	31
	No	82 (78.8)	77 (83.7)	159 (81.1)
	Yes	22 (21.2)	15 (16.3)	37 (18.9)
GDM IADPSG CRITERIA CODED$ (n(%))	Missing	14	17	31
	GDM first at visit 5 (28 weeks)	14 (13.5)	5 (5.4)	19 (9.7)
	GDM first at visit 6 (36 weeks)	8 (7.7)	10 (10.9)	18 (9.2)
	NO GDM	82 (78.8)	77 (83.7)	159 (81.1)

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Once GDM is present in visit 5 then it will stay present in visit 6
#WHO criteria: Fasting glucose >= 7.0 mmol/l or 2hr glucose >=7.8 mmol/l
$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.2 Gestational diabetes mellitus (GDM) IADPSG$ - OGTT Test*- Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of GDM_IAD by AllocatedTreatment*

GDM_IAD(GDM calculated using IADPSG criteria (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Missing	17	14	.
No	77	82	159
Yes	15	22	37
Total	92	104	196

Frequency Missing = 31

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
GDMIAD_pp	AllocatedTreatment METFORMIN vs PLACEBO	0.726	0.351	1.501	0.3877	0.4655

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47

By: Aryelly Rodriguez - ECTU Statistician

Summary statistics are presented in table 5.1.6.1 of this report

*Analised using logistic regression (binary logit), probability modeled GDM_IAD='Yes'

#Significance level set at p<0.05. Detailed analysis in file 'Empowar_5_1_6_glucose_GDM_analysis.lst'

$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.3 Gestational diabetes mellitus (GDM) IADPSG$ - OGTT Test*- Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency

Table of GDM_CODE_IAD by AllocatedTreatment

GDM_CODE_IAD(GDM calculated using IADPSG criteria by visit)	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Missing	17	14	.
GDM first at visit 5 (28 weeks)	5	14	19
GDM first at visit 6 (36 weeks)	10	8	18
NO GDM	77	82	159
Total	92	104	196

Frequency Missing = 31

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 5.1.6.1 of this report
*Analised using The Mantel-Haenszel chi-square statistic tests
#Significance level set at p<0.05. Detailed analysis in file 'Empowar_5_1_6_glucose_GDM_analysis.lst'
$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.1.6.3 Gestational diabetes mellitus (GDM) IADPSG$ - OGTT Test*- Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Statistics for Table of GDM_CODE_IAD by AllocatedTreatment

Statistic	*DF*	*Value*	*Prob*
Chi-Square	2	3.9226	0.1407
Likelihood Ratio Chi-Square	2	4.0837	0.1298
Mantel-Haenszel Chi-Square	1	2.0234	0.1549
Phi Coefficient		0.1415	
Contingency Coefficient		0.1401	
Cramer's V		0.1415	

Effective Sample Size = 196
Frequency Missing = 31

WARNING: 14 % of the data are missing.

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47
Summary statistics are presented in table 5.1.6.1 of this report
*Analised using The Mantel-Haenszel chi-square statistic tests
#Significance level set at p<0.05. Detailed analysis in file 'Empowar_5_1_6_glucose_GDM_analysis.lst'
$IADPSG criteria: Fasting glucose >= 5.1 mmol/l or 2hr glucose >= 8.5 mmol/l

By: Aryelly Rodriguez - ECTU Statistician

Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.1 Insulin - Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Insulin - Visit 2 (mIU/ml)	Mean	22.963	21.915	22.464
	Median	20.823	20.557	20.773
	SD	10.462	8.996	9.779
	MIN,MAX	7.43,71.22	2.00,45.46	2.00,71.22
	Q1,Q3	16.50,27.27	15.64,26.94	15.81,27.27
	n	101	92	193
	Nmiss	17	17	34
Insulin - Visit 5 (mIU/ml)	Mean	28.073	24.539	26.371
	Median	24.360	22.995	23.810
	SD	13.285	12.181	12.854
	MIN,MAX	9.82,89.98	6.82,91.05	6.82,91.05
	Q1,Q3	19.74,31.85	16.95,29.19	18.05,30.73
	n	99	92	191
	Nmiss	19	17	36

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.1 Insulin - Visit 6 (36 Weeks) (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Insulin - Visit 6 (mIU/ml)	Mean	31.886	32.588	32.218
	Median	29.134	27.088	28.632
	SD	13.402	26.065	20.334
	MIN,MAX	10.10,91.87	9.78,204.26	9.78,204.26
	Q1,Q3	22.44,37.46	17.65,37.34	20.83,37.34
	n	88	79	167
	Nmiss	30	30	60

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.2.1 Fasted Insulin - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Insulin_log_visit_6 - pp	3.502	0.0860	88	3.438	0.0831	79	-0.063	-0.199	0.072	0.851	0.3576

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Summary statistics are presented in table 5.2.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed insulin in blood by allocated treatment,
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log transformed mean and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_2_2_INSULIN_RES_outcome_analysis.lst'
Parameter shown normal or near-normal behavior

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.2.2.2 Fasted Insulin - Visit 5 (28 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Insulin_log_visit_5 - pp	3.323	0.0737	99	3.185	0.0696	92	-0.138	-0.251	-0.025	5.772	0.0173

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Summary statistics are presented in table 5.2.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed insulin in blood by allocated treatment,
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log transformed mean and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_2_2_INSULIN_RES_outcome_analysis_v5'.lst
Parameter shown normal or near-normal behavior

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.1 HOMA-IR - Visit 2 Consent/Baseline (10-16 Weeks) and Visit 5 (28 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
HOMA - visit 2 - base	Mean	4.592	4.338	4.471
	Median	3.954	3.966	3.961
	SD	2.322	1.824	2.098
	MIN,MAX	1.16,14.24	0.34,8.93	0.34,14.24
	Q1,Q3	3.09,5.54	3.10,5.44	3.09,5.53
	n	101	92	193
	Nmiss	17	17	34
HOMA - visit 5 - base	Mean	5.683	4.812	5.261
	Median	4.902	4.650	4.754
	SD	2.986	2.544	2.808
	MIN,MAX	1.83,18.99	1.23,19.42	1.23,19.42
	Q1,Q3	3.82,6.56	3.09,6.01	3.37,6.23
	n	98	92	190
	Nmiss	20	17	37

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.2 HOMA-IR - Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
HOMA - visit 6 - base	Mean	6.362	6.222	6.297
	Median	5.809	5.056	5.358
	SD	2.963	4.904	3.976
	MIN,MAX	1.62,16.74	1.74,34.50	1.62,34.50
	Q1,Q3	4.40,7.42	3.40,7.16	3.71,7.31
	n	88	77	165
	Nmiss	30	32	62

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.3.1 HOMA_IR - VISIT 6 (36 WEEKS) - Statistical Analysis

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
HOMA-IR_log_visit_6 - pp	1.876	0.0947	88	1.784	0.0920	77	-0.092	-0.243	0.059	1.459	0.2290

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Summary statistics are presented in table 5.3.2 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed HOMA-IR in blood by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_3_4_glucose_outcome_analysis.lst'
Parameter shown normal or near-normal behavior

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DOI: 10.3310/eme03070

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.3.2 HOMA_IR - VISIT 5 (28 WEEKS) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
HOMA-IR_log_visit_5 - pp	1.692	0.0816	98	1.527	0.0770	92	-0.165	-0.290	-0.039	6.726	0.0103

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 5.3.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed HOMA-IR in blood by allocated treatment,
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_3_4_glucose_outcome_analysis_5v.lst'
Parameter shown normal or near-normal behavior

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.1 HOMA-IR - Visit 5 (28 Weeks) split by C-section

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - HOMA_IR - V5 - base	Mean	5.85	5.39	5.64
	Median	5.37	5.25	5.25
	SD	2.61	3.19	2.87
	MIN,MAX	2.6,13.4	1.9,19.4	1.9,19.4
	Q1,Q3	3.8,7.1	3.3,6.2	3.7,6.8
	n	35	29	64
	Nmiss	8	2	10
No C-section - HOMA_IR - V5 - base	Mean	5.59	4.54	5.07
	Median	4.69	4.30	4.59
	SD	3.19	2.18	2.78
	MIN,MAX	1.8,19.0	1.2,11.3	1.2,19.0
	Q1,Q3	3.5,6.3	3.0,5.7	3.2,5.8
	n	63	62	125
	Nmiss	12	15	27

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.2 HOMA-IR - Visit 6 (36 Weeks) split by C-section

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Yes C-section - HOMA_IR - V6 - base	Mean	6.79	5.10	6.11
	Median	6.23	5.06	5.40
	SD	3.06	2.03	2.80
	MIN,MAX	2.7,13.8	1.7,9.5	1.7,13.8
	Q1,Q3	4.7,8.0	3.3,6.7	4.1,7.2
	n	33	22	55
	Nmiss	10	7	17
No C-section - HOMA_IR - V6 - base	Mean	6.10	6.67	6.39
	Median	5.60	4.99	5.32
	SD	2.90	5.61	4.46
	MIN,MAX	1.6,16.7	1.9,34.5	1.6,34.5
	Q1,Q3	4.1,7.4	3.4,7.9	3.6,7.5
	n	55	55	110
	Nmiss	20	22	42

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_HOMA_IR_V5_base	Mean	4.04	2.34	3.19
	Median	4.04	2.34	3.19
	SD	.	.	1.20
	MIN,MAX	4.0,4.0	2.3,2.3	2.3,4.0
	Q1,Q3	4.0,4.0	2.3,2.3	2.3,4.0
	n	1	1	2
	Nmiss	0	0	0
5%<=_HOMA_IR_V5_base	Mean	3.85	2.88	3.36
	Median	4.04	2.83	3.14
	SD	0.94	0.56	0.88
	MIN,MAX	2.8,4.7	2.3,3.5	2.3,4.7
	Q1,Q3	2.8,4.7	2.3,3.5	2.8,4.0
	n	3	3	6
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_HOMA_IR_V5_base	Mean	4.72	3.77	4.29
	Median	4.81	3.44	4.04
	SD	1.23	1.75	1.49
	MIN,MAX	2.8,6.5	2.3,6.8	2.3,6.8
	Q1,Q3	4.0,5.4	2.8,3.5	2.8,5.4
	n	6	5	11
	Nmiss	0	1	1
10%> AND 90%<=_HOMA_IR_V5_base	Mean	5.53	4.65	5.11
	Median	4.62	4.65	4.64
	SD	2.98	2.09	2.62
	MIN,MAX	1.8,19.0	1.2,11.3	1.2,19.0
	Q1,Q3	3.7,6.4	3.1,5.6	3.3,6.1
	n	75	68	143
	Nmiss	15	13	28

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_HOMA_IR_V5_base	Mean	6.72	5.71	6.20
	Median	5.78	5.56	5.77
	SD	3.31	3.92	3.62
	MIN,MAX	2.7,14.8	1.5,19.4	1.5,19.4
	Q1,Q3	4.9,7.0	3.1,6.9	4.3,6.9
	n	17	18	35
	Nmiss	4	3	7
95%>_HOMA_IR_V5_base	Mean	5.37	5.82	5.64
	Median	5.74	4.94	5.53
	SD	1.34	4.68	3.66
	MIN,MAX	2.7,7.0	1.5,19.4	1.5,19.4
	Q1,Q3	4.7,6.2	3.0,6.9	3.9,6.7
	n	8	12	20
	Nmiss	4	0	4

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.3 HOMA-IR - Visit 5 (28 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_HOMA_IR_V5_base	Mean	5.74	6.54	6.27
	Median	5.74	5.15	5.73
	SD	0.67	5.54	4.45
	MIN,MAX	4.9,6.6	1.5,19.4	1.5,19.4
	Q1,Q3	5.3,6.2	3.6,6.9	4.5,6.7
	n	4	8	12
	Nmiss	3	0	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
3%<=_HOMA_IR_V6_base	Mean	2.14	.	2.14
	Median	2.14	.	2.14
	SD	.	.	.
	MIN,MAX	2.1,2.1	.,.	2.1,2.1
	Q1,Q3	2.1,2.1	.,.	2.1,2.1
	n	1	0	1
	Nmiss	0	1	1
5%<=_HOMA_IR_V6_base	Mean	3.07	3.64	3.30
	Median	3.51	3.64	3.51
	SD	0.81	0.92	0.80
	MIN,MAX	2.1,3.6	3.0,4.3	2.1,4.3
	Q1,Q3	2.1,3.6	3.0,4.3	3.0,3.6
	n	3	2	5
	Nmiss	0	1	1

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
10%<=_HOMA_IR_V6_base	Mean	5.50	4.56	5.08
	Median	3.57	4.00	3.72
	SD	3.61	1.87	2.84
	MIN,MAX	2.1,11.0	3.0,7.3	2.1,11.0
	Q1,Q3	3.5,7.3	3.4,5.8	3.5,7.3
	n	5	4	9
	Nmiss	1	2	3
10%> AND 90%<=_HOMA_IR_V6_base	Mean	6.00	6.58	6.27
	Median	5.60	5.11	5.34
	SD	2.57	5.44	4.13
	MIN,MAX	1.6,14.0	1.9,34.5	1.6,34.5
	Q1,Q3	4.4,6.8	3.3,7.4	3.7,7.2
	n	69	58	127
	Nmiss	21	22	43

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
90%>_HOMA_IR_V6_base	Mean	8.44	5.26	6.80
	Median	7.57	4.63	6.30
	SD	3.81	2.61	3.57
	MIN,MAX	3.6,16.7	1.7,10.0	1.7,16.7
	Q1,Q3	5.0,11.9	3.5,6.5	4.1,8.3
	n	14	15	29
	Nmiss	7	5	12
95%>_HOMA_IR_V6_base	Mean	8.25	4.71	6.13
	Median	7.57	4.11	6.05
	SD	3.34	2.73	3.39
	MIN,MAX	4.8,12.7	1.7,10.0	1.7,12.7
	Q1,Q3	5.0,11.9	2.3,6.3	3.5,7.8
	n	6	9	15
	Nmiss	6	2	8

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

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Section 5. Maternal insulin resistance (Secondary Outcome)

5.3.4.4 HOMA-IR - Visit 6 (36 Weeks) split by birth centile

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
97%>_HOMA_IR_V6_base	Mean	8.44	5.15	5.98
	Median	8.44	5.20	5.66
	SD	4.84	3.09	3.53
	MIN,MAX	5.0,11.9	1.7,10.0	1.7,11.9
	Q1,Q3	5.0,11.9	2.3,6.5	3.2,8.3
	n	2	6	8
	Nmiss	5	1	6

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose_base x insulin / 22.5)

Section 5. Laboratory results (Secondary Outcome)

5.4.1 NEFA by study visit

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
NEFA - visit 2* (mmol/L)	Mean	0.544	0.468	0.508
	Median	0.520	0.440	0.480
	SD	0.202	0.161	0.187
	MIN,MAX	0.16,1.35	0.13,0.82	0.13,1.35
	Q1,Q3	0.40,0.66	0.35,0.59	0.37,0.63
	n	101	92	193
	Nmiss	17	17	34
NEFA - visit 5* (mmol/L)	Mean	0.428	0.441	0.434
	Median	0.440	0.410	0.440
	SD	0.135	0.165	0.150
	MIN,MAX	0.11,0.78	0.12,0.86	0.11,0.86
	Q1,Q3	0.31,0.52	0.33,0.54	0.32,0.53
	n	99	92	191
	Nmiss	19	17	36

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.1 NEFA by study visit (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
NEFA - visit 6* (mmol/L)	Mean	0.465	0.481	0.472
	Median	0.445	0.470	0.460
	SD	0.194	0.207	0.200
	MIN,MAX	0.13,0.97	0.11,1.00	0.11,1.00
	Q1,Q3	0.31,0.60	0.31,0.62	0.31,0.60
	n	88	79	167
	Nmiss	30	30	60

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

Section 5. Laboratory results (Secondary Outcome)

5.4.2 IL_6 by study visit

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
IL_6 - visit 2* (pg/ml)	Mean	2.304	2.031	2.174
	Median	2.020	1.823	1.911
	SD	1.120	1.108	1.120
	MIN,MAX	0.80,7.21	0.62,8.14	0.62,8.14
	Q1,Q3	1.50,2.88	1.39,2.31	1.45,2.55
	n	101	92	193
	Nmiss	17	17	34
IL_6 - visit 5* (pg/ml)	Mean	2.456	2.288	2.375
	Median	2.093	2.087	2.093
	SD	1.261	1.192	1.228
	MIN,MAX	0.80,7.72	0.88,8.76	0.80,8.76
	Q1,Q3	1.62,3.08	1.60,2.69	1.62,2.86
	n	99	92	191
	Nmiss	19	17	36

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.2 IL_6 by study visit (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
IL_6 - visit 6* (pg/ml)	Mean	3.659	2.774	3.240
	Median	2.753	2.291	2.567
	SD	3.733	1.264	2.872
	MIN,MAX	1.19,29.94	1.11,7.35	1.11,29.94
	Q1,Q3	2.14,3.73	1.91,3.38	2.01,3.64
	n	88	79	167
	Nmiss	30	30	60

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

Section 5. Laboratory results (Secondary Outcome)

5.4.3 Leptin by study visit

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Leptin - visit 2* (ng/ml)	Mean	90.659	99.787	95.010
	Median	82.244	91.700	87.270
	SD	46.173	39.236	43.139
	MIN,MAX	24.19,305.25	33.04,250.68	24.19,305.25
	Q1,Q3	58.41,105.04	74.23,115.62	66.74,112.67
	n	101	92	193
	Nmiss	17	17	34
Leptin - visit 5* (ng/ml)	Mean	100.761	98.464	99.654
	Median	93.404	87.486	91.854
	SD	49.942	40.053	45.345
	MIN,MAX	25.94,376.10	27.14,212.98	25.94,376.10
	Q1,Q3	66.81,117.12	69.59,125.97	68.27,124.41
	n	99	92	191
	Nmiss	19	17	36

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.3 Leptin by study visit (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Leptin - visit 6* (ng/ml)	Mean	103.798	101.257	102.596
	Median	92.129	88.806	91.308
	SD	55.337	47.019	51.433
	MIN,MAX	22.67,397.20	33.78,255.00	22.67,397.20
	Q1,Q3	69.61,128.54	66.98,122.46	68.78,127.27
	n	88	79	167
	Nmiss	30	30	60

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

Section 5. Laboratory results (Secondary Outcome)

5.4.4 Cortisol by study visit

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Cortisol - visit 2* (nmol/l)	Mean	384.760	438.183	410.226
	Median	369.660	409.711	375.366
	SD	135.506	186.538	163.619
	MIN,MAX	164.06,733.26	150.26,1197.1	150.26,1197.1
	Q1,Q3	279.72,476.13	292.00,546.21	288.03,506.95
	n	101	92	193
	Nmiss	17	17	34
Cortisol - visit 5* (nmol/l)	Mean	708.183	802.516	753.621
	Median	627.150	751.033	702.800
	SD	230.255	263.424	250.628
	MIN,MAX	395.60,1922.5	234.30,1826.3	234.30,1922.5
	Q1,Q3	547.84,809.18	654.20,930.33	594.08,893.09
	n	99	92	191
	Nmiss	19	17	36

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 5 (28 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.4 Cortisol by study visit (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Cortisol - visit 6* (nmol/l)	Mean	806.477	888.378	845.220
	Median	778.645	842.706	800.754
	SD	225.004	250.727	240.321
	MIN,MAX	432.38,1903.3	432.71,1859.6	432.38,1903.3
	Q1,Q3	659.11,884.97	694.70,1022.1	675.39,967.38
	n	88	79	167
	Nmiss	30	30	60

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 6 (36 Weeks)

Section 5. Laboratory results (Secondary Outcome)

5.4.5 PAI1/PAI2 ratio by study visit

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
PAI_ratio - visit 2*	Mean	1.550	2.158	1.838
	Median	1.084	0.986	1.044
	SD	1.563	6.493	4.607
	MIN,MAX	0.28,11.89	0.33,57.63	0.28,57.63
	Q1,Q3	0.78,1.73	0.74,1.47	0.76,1.58
	n	91	82	173
	Nmiss	27	27	54
PAI_ratio - visit 6*	Mean	3.396	3.314	3.357
	Median	2.637	1.864	2.296
	SD	2.651	3.090	2.859
	MIN,MAX	0.64,13.98	0.68,16.41	0.64,16.41
	Q1,Q3	1.44,4.70	1.24,4.23	1.34,4.52
	n	91	82	173
	Nmiss	27	27	54

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Visit 2 Consent/Baseline (10-16 Weeks), Visit 6 (36 Weeks)

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Section 5. Laboratory results (Secondary Outcome)

5.4.6 NEFA, IL-6, Leptin, Cortisol, PAI1/PAI2 ratio Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
IL_6_log_Visit6 - pp	1.056	0.0892	88	0.903	0.0861	79	-0.153	-0.294	-0.012	4.613	0.0333
Leptin_log_Visit6 - pp	4.521	0.0812	88	4.528	0.0784	79	0.007	-0.121	0.135	0.011	0.9152
Cortisol_nmol_l_log_Visit6 - pp	6.639	0.0497	88	6.727	0.0480	79	0.088	0.010	0.167	4.913	0.0281
NEFA_log_Visit6 - pp	-0.776	0.0790	88	-0.736	0.0763	79	0.040	-0.085	0.165	0.406	0.5249
PAI_ratio_log_Visit6 - pp	1.009	0.1442	91	0.899	0.1339	82	-0.110	-0.328	0.107	1.009	0.3167

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Summary statistics are presented in tables 5.4.1 to 5.4.5 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_4_other_labs_analysis_v6.lst'
All parameters shown normal or near-normal behavior

Section 5. Laboratory results (Secondary Outcome)

5.5.1 B12# - Visit 2 Consent/Baseline (10-16 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
B12 (ng/l) - visit 2	Mean	256.6	259.4	257.9
	Median	240.5	246.0	245.0
	SD	108.1	71.6	92.3
	MIN,MAX	55,760	80,404	55,760
	Q1,Q3	191,324	214,306	205,314
	n	90	82	172
	Nmiss	28	27	55
B12 below 95th - visit 2 (n(%))*	Missing	28	27	55
	Yes	82 (91.1)	78 (95.1)	160 (93.0)
	No	8 (8.9)	4 (4.9)	12 (7.0)
B12 below 5th - visit 2 (n(%))*	Missing	28	27	55
	Yes	6 (6.7)	4 (4.9)	10 (5.8)
	No	84 (93.3)	78 (95.1)	162 (94.2)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*5th centile was set at 117 ng/l and 95th centile was set at 389 ng/l
#Reference range 200-940 ng/l

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Section 5. Laboratory results (Secondary Outcome)

5.5.1 B12# - Visit 6 (36 Weeks)(Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
B12 (ng/l) - visit 6	Mean	226.1	205.5	216.1
	Median	224.5	198.0	206.0
	SD	75.4	68.6	72.7
	MIN,MAX	60,482	47,417	47,482
	Q1,Q3	176,275	162,244	168,253
	n	88	83	171
	Nmiss	30	26	56
B12 below 95th - visit 6 (n(%))*	Missing	30	26	56
	Yes	85 (96.6)	82 (98.8)	167 (97.7)
	No	3 (3.4)	1 (1.2)	4 (2.3)
B12 below 5th - visit 6 (n(%))*	Missing	30	26	56
	Yes	5 (5.7)	6 (7.2)	11 (6.4)
	No	83 (94.3)	77 (92.8)	160 (93.6)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*5th centile was set at 117 ng/l and 95th centile was set at 389 ng/l

#Reference range 200-940 ng/l

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Section 5. Laboratory results (Secondary Outcome)

5.5.2 Serum folate# - Visit 2 Consent/Baseline (10-16 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Serum Folate (ug/l) - visit 2	Mean	13.93	14.48	14.19
	Median	17.00	16.85	16.85
	SD	4.56	4.37	4.46
	MIN,MAX	4.3,17.5	2.4,21.0	2.4,21.0
	Q1,Q3	10.5,17.5	12.2,17.5	11.2,17.5
	n	90	82	172
	Nmiss	28	27	55
Serum Folate below 95th - visit 2 (n(%))*	Missing	28	27	55
	Yes	45 (50.0)	46 (56.1)	91 (52.9)
	No	45 (50.0)	36 (43.9)	81 (47.1)
Serum Folate below 5th - visit 2 (n(%))*	Missing	28	27	55
	Yes	0	1 (1.2)	1 (0.6)
	No	90 (100)	81 (98.8)	171 (99.4)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*5th centile was set at 2.6 ug/l and 95th centile was set at 17.5 ug/l
#Reference range 3.1-17.5 ug/l, if Serum folate value was reported as greater than 17.5 ug/l, then the value was imputed at 17.5 ug/l for summarisation

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Section 5. Laboratory results (Secondary Outcome)

5.5.2 Serum folate# - Visit 6 (36 Weeks) (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Serum Folate (ug/l) - visit 6	Mean	9.15	9.46	9.30
	Median	6.95	7.40	7.30
	SD	6.01	5.72	5.86
	MIN,MAX	1.3,17.5	1.2,21.0	1.2,21.0
	Q1,Q3	3.8,16.3	4.2,15.2	4.1,16.1
	n	90	83	173
	Nmiss	28	26	54
Serum Folate below 95th - visit 6 (n(%))*	Missing	28	26	54
	Yes	70 (77.8)	66 (79.5)	136 (78.6)
	No	20 (22.2)	17 (20.5)	37 (21.4)
Serum Folate below 5th - visit 6 (n(%))*	Missing	28	26	54
	Yes	7 (7.8)	5 (6.0)	12 (6.9)
	No	83 (92.2)	78 (94.0)	161 (93.1)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*5th centile was set at 2.6 ug/l and 95th centile was set at 17.5 ug/l

#Reference range 3.1-17.5 ug/l, if Serum folate value was reported as greater than 17.5 ug/l, then the value was imputed at 17.5 ug/l for summarisation

Section 5. Laboratory results (Secondary Outcome)

5.5.3 B12 and Serum Folate Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
B12_log_99_Visit6 - pp	5.401	0.0669	88	5.284	0.0619	83	-0.117	-0.218	-0.015	5.134	0.0248
SFOLATE_log_99_Visit6 - pp	1.946	0.1428	90	2.054	0.1327	83	0.108	-0.109	0.325	0.970	0.3263

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Summary statistics are presented in tables 5.5.2 and 5.6.2 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_5_B12_folate_continuo_analysis_v6.lst'
All parameters shown normal or near-normal behavior

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Section 5. Laboratory results (Secondary Outcome)

5.5.4.1 B12* - Patients below 5th centile - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of B12_N5TH by AllocatedTreatment*

B12_N5TH(Patients with B12 below 5th centile (Y/N))	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
Missing	26	30	.
Yes	6	5	11
No	77	83	160
Total	83	88	171

Frequency Missing = 56

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
b12_n5th_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.294	0.379	4.411	0.6809	0.7614

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*Analised using logistic regression (binary logit), probability modeled is B12_N5THb='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_5_5_B12_folate_discre_analysis_v6.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 5. Laboratory results (Secondary Outcome)

5.5.4.2 Serum Folate* - Patients below 5th centile - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of SFOL_N5TH by AllocatedTreatment*

SFOL_N5TH(Patients with Serum Folate below 5th centile (Y/N))	*AllocatedTreatment(Allocated Treatment)* *METFORMIN*	*PLACEBO*	*Total*
Missing	26	28	.
Yes	5	7	12
No	78	83	161
Total	83	90	173

Frequency Missing = 54

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
sfol_n5th_pp	AllocatedTreatment METFORMIN vs PLACEBO	0.760	0.232	2.495	0.6510	0.7686

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By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is SFOL_N5THb='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_5_5_B12_folate_discre_analysis_v6.lst'

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Section 6. Mother Anthropometry

6.1.1 Maternal Height at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Height (cm) at Visit 2	Mean	166.1	165.8	166.0
	Median	166.2	165.5	166.0
	SD	6.0	5.7	5.9
	MIN,MAX	152,184	153,180	152,184
	Q1,Q3	162,170	162,170	162,170
	n	118	109	227
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.1.2 Maternal Height at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Height (cm) at Visit 6	Mean	166.2	166.4	166.3
	Median	166.0	166.5	166.5
	SD	6.1	5.7	5.9
	MIN,MAX	152,184	155,183	152,184
	Q1,Q3	162,170	163,170	162,170
	n	105	94	199
	Nmiss	13	15	28
Height (cm) change V6 baseline	Mean	0.2	0.1	0.2
	Median	0.0	0.0	0.0
	SD	0.8	0.8	0.8
	MIN,MAX	-2,2	-3,3	-3,3
	Q1,Q3	0,0	0,0	0,0
	n	105	94	199
	Nmiss	13	15	28

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.1.3 Maternal Height at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Height (cm) at Visit 9	Mean	165.6	166.2	165.9
	Median	166.0	166.0	166.0
	SD	6.0	5.7	5.8
	MIN,MAX	152,184	155,180	152,184
	Q1,Q3	162,169	162,170	162,170
	n	89	89	178
	Nmiss	29	20	49
Height (cm) change V9 baseline	Mean	-0.2	-0.1	-0.1
	Median	0.0	0.0	0.0
	SD	0.7	0.7	0.7
	MIN,MAX	-3,2	-2,3	-3,3
	Q1,Q3	0,0	0,0	0,0
	n	89	89	178
	Nmiss	29	20	49

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.2.1 Maternal Weight at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Weight (kg) at Visit 2	Mean	103.74	104.04	103.88
	Median	98.33	104.00	101.30
	SD	16.95	15.22	16.10
	MIN,MAX	75.6,154.0	74.0,140.3	74.0,154.0
	Q1,Q3	90.6,114.6	93.3,115.0	92.0,115.0
	n	118	109	227
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.2.2.1 Maternal Weight at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Weight (kg) at Visit 6	Mean	111.32	111.97	111.62
	Median	106.45	111.00	109.70
	SD	17.51	15.75	16.67
	MIN,MAX	79.8,159.0	79.1,165.7	79.1,165.7
	Q1,Q3	98.2,123.0	103.9,120.0	100.0,121.0
	n	106	93	199
	Nmiss	12	16	28
Weight (kg) change V6 baseline	Mean	7.40	6.85	7.14
	Median	6.95	6.50	6.80
	SD	4.56	6.11	5.34
	MIN,MAX	-4.5,18.8	-5.7,35.7	-5.7,35.7
	Q1,Q3	4.8,9.5	3.2,10.0	3.9,9.7
	n	106	93	199
	Nmiss	12	16	28

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.2.2.2 Maternal Weight at Visit 6 (36 Weeks) change from baseline - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Weight-DIFF-Visit_6 - pp	6.932	0.8458	106	6.593	0.8087	93	-0.339	-1.769	1.091	0.218	0.6408

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Summary statistics are presented in table 6.2.2.1 of this report
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the means for the Weight Difference by allocated treatment,
SE represents standard error of the estimated means and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_6_2_2_Mother Anthropometry_weight_gain_v6.lst'
Parameter shown normal or near-normal behavior

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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.2.3 Maternal Weight at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Weight (kg) at Visit 9	Mean	102.04	105.07	103.54
	Median	98.20	104.57	101.20
	SD	15.69	18.53	17.17
	MIN,MAX	72.7,143.0	73.8,193.0	72.7,193.0
	Q1,Q3	92.0,112.0	94.5,112.2	92.3,112.1
	n	89	87	176
	Nmiss	29	22	51
Weight (kg) change V9 baseline	Mean	0.05	0.83	0.44
	Median	0.00	-0.80	-0.30
	SD	6.08	10.95	8.81
	MIN,MAX	-13.6,18.2	-19.2,79.5	-19.2,79.5
	Q1,Q3	-3.5,3.7	-4.0,2.7	-3.6,3.2
	n	89	87	176
	Nmiss	29	22	51

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.3.1 Maternal Waist at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Waist (cm) at Visit 2	Mean	108.3	108.6	108.4
	Median	106.0	108.6	107.0
	SD	12.6	11.2	11.9
	MIN,MAX	85,148	84,134	84,148
	Q1,Q3	99,118	101,117	100,117
	n	118	109	227
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.3.2 Maternal Waist at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Waist (cm) at Visit 6	Mean	119.0	117.4	118.3
	Median	117.3	117.0	117.0
	SD	12.6	10.9	11.9
	MIN,MAX	95,161	88,140	88,161
	Q1,Q3	108,127	109,126	109,126
	n	106	93	199
	Nmiss	12	16	28
Waist (cm) change V6 baseline	Mean	10.3	9.0	9.7
	Median	10.0	9.0	9.0
	SD	7.4	8.2	7.8
	MIN,MAX	-10,29	-22,28	-22,29
	Q1,Q3	5,15	4,13	5,14
	n	106	93	199
	Nmiss	12	16	28

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.3.3 Maternal Waist at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Waist (cm) at Visit 9	Mean	108.4	109.3	108.9
	Median	106.0	109.0	107.0
	SD	13.0	13.2	13.0
	MIN,MAX	80,142	79,141	79,142
	Q1,Q3	99,115	100,117	100,117
	n	88	89	177
	Nmiss	30	20	50
Waist (cm) change V9 baseline	Mean	0.9	1.0	0.9
	Median	0.3	1.0	0.5
	SD	7.6	8.2	7.8
	MIN,MAX	-21,22	-25,23	-25,23
	Q1,Q3	-4,5	-4,5	-4,5
	n	88	89	177
	Nmiss	30	20	50

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.4.1 Maternal Hip at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Hip (cm) at Visit 2	Mean	126.8	127.5	127.1
	Median	125.0	126.0	125.0
	SD	11.6	12.2	11.9
	MIN,MAX	104,155	100,155	100,155
	Q1,Q3	118,134	119,136	119,134
	n	118	109	227
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.4.2 Maternal Hip at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Hip (cm) at Visit 6	Mean	129.8	131.1	130.4
	Median	128.3	130.0	129.5
	SD	11.9	11.8	11.8
	MIN,MAX	108,158	107,174	107,174
	Q1,Q3	122,139	123,140	122,139
	n	106	93	199
	Nmiss	12	16	28
Hip (cm) change V6 baseline	Mean	2.9	3.0	2.9
	Median	2.8	2.5	2.5
	SD	6.0	6.5	6.2
	MIN,MAX	-11,18	-12,20	-12,20
	Q1,Q3	-1,6	-1,7	-1,7
	n	106	93	199
	Nmiss	12	16	28

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.4.3 Maternal Hip at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Hip (cm) at Visit 9	Mean	127.1	127.7	127.4
	Median	126.0	127.0	126.0
	SD	12.0	13.4	12.7
	MIN,MAX	99,154	79,167	79,167
	Q1,Q3	121,135	121,133	121,134
	n	88	89	177
	Nmiss	30	20	50
Hip (cm) change V9 baseline	Mean	0.9	-0.3	0.3
	Median	1.0	0.0	1.0
	SD	6.9	8.1	7.5
	MIN,MAX	-19,17	-41,16	-41,17
	Q1,Q3	-3,6	-5,5	-4,6
	n	88	89	177
	Nmiss	30	20	50

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.5.1 Maternal Mid Arm at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Mid Arm (cm) at Visit 2	Mean	36.6	37.0	36.8
	Median	36.0	37.0	36.0
	SD	4.8	4.4	4.6
	MIN,MAX	22,48	28,52	22,52
	Q1,Q3	34,39	34,39	34,39
	n	117	106	223
	Nmiss	1	3	4

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.5.2 Maternal Mid Arm at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Mid Arm (cm) at Visit 6	Mean	36.4	36.4	36.4
	Median	36.0	36.0	36.0
	SD	4.7	4.4	4.6
	MIN,MAX	22,48	22,52	22,52
	Q1,Q3	34,39	34,39	34,39
	n	105	93	198
	Nmiss	13	16	29
Mid Arm (cm) change V6 baseline	Mean	-0.3	-1.1	-0.7
	Median	-0.4	-1.0	-0.5
	SD	3.6	4.0	3.8
	MIN,MAX	-10,12	-20,9	-20,12
	Q1,Q3	-2,1	-2,1	-2,1
	n	104	92	196
	Nmiss	14	17	31

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.5.3 Maternal Mid Arm at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Mid Arm (cm) at Visit 9	Mean	37.2	37.0	37.1
	Median	36.8	37.0	37.0
	SD	4.6	4.2	4.4
	MIN,MAX	28,52	28,54	28,54
	Q1,Q3	35,40	34,40	34,40
	n	87	89	176
	Nmiss	31	20	51
Mid Arm (cm) change V9 baseline	Mean	0.8	-0.2	0.3
	Median	0.5	0.0	0.0
	SD	4.5	3.6	4.1
	MIN,MAX	-7,25	-9,7	-9,25
	Q1,Q3	-2,3	-3,2	-2,3
	n	86	87	173
	Nmiss	32	22	54

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
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Section 6. Mother Anthropometry

6.6.1 Maternal Mid Thigh at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Mid Thigh (cm) at Visit 2	Mean	64.2	65.3	64.8
	Median	64.3	64.0	64.0
	SD	7.3	7.0	7.2
	MIN,MAX	25,84	50,86	25,86
	Q1,Q3	60,69	61,69	60,69
	n	116	106	222
	Nmiss	2	3	5

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.6.2 Maternal Mid Thigh at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Mid Thigh (cm) at Visit 6	Mean	64.8	65.7	65.2
	Median	65.0	65.0	65.0
	SD	7.2	6.6	6.9
	MIN,MAX	29,80	53,83	29,83
	Q1,Q3	60,70	60,70	60,70
	n	105	93	198
	Nmiss	13	16	29
Mid Thigh (cm) change V6 baseline	Mean	0.5	0.1	0.3
	Median	0.0	1.0	0.5
	SD	4.5	5.1	4.8
	MIN,MAX	-10,14	-16,14	-16,14
	Q1,Q3	-3,4	-4,3	-3,3
	n	103	91	194
	Nmiss	15	18	33

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Section 6. Mother Anthropometry

6.6.3 Maternal Mid Thigh at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Mid Thigh (cm) at Visit 9	Mean	64.7	65.7	65.2
	Median	64.8	65.0	65.0
	SD	6.3	6.7	6.5
	MIN,MAX	51,84	52,84	51,84
	Q1,Q3	60,68	61,70	61,70
	n	86	88	174
	Nmiss	32	21	53
Mid Thigh (cm) change V9 baseline	Mean	1.1	0.5	0.8
	Median	0.5	1.0	1.0
	SD	7.0	5.7	6.4
	MIN,MAX	-10,47	-19,21	-19,47
	Q1,Q3	-2,4	-3,4	-3,4
	n	84	86	170
	Nmiss	34	23	57

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Section 6. Mother Anthropometry

6.7.1 Maternal Tricep Skinfold at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Tricep Skinfold (mm) at Visit 2	Mean	33.3	32.6	33.0
	Median	31.2	31.5	31.2
	SD	9.4	9.7	9.5
	MIN,MAX	15,62	10,66	10,66
	Q1,Q3	27,40	26,39	27,39
	n	117	108	225
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.7.2 Maternal Tricep Skinfold at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Tricep Skinfold (mm) at Visit 6	Mean	31.4	33.4	32.3
	Median	32.0	31.5	32.0
	SD	9.4	11.5	10.4
	MIN,MAX	11,65	11,80	11,80
	Q1,Q3	24,36	26,39	25,38
	n	106	94	200
	Nmiss	12	15	27
Tricep Skinfold (mm) change V6 baseline	Mean	-1.9	0.4	-0.8
	Median	-1.0	0.0	-0.4
	SD	9.1	12.3	10.7
	MIN,MAX	-31,24	-44,34	-44,34
	Q1,Q3	-6,3	-6,6	-6,4
	n	105	93	198
	Nmiss	13	16	29

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.7.3 Maternal Tricep Skinfold at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Tricep Skinfold (mm) at Visit 9	Mean	33.1	33.8	33.5
	Median	32.6	31.0	32.3
	SD	11.0	12.6	11.8
	MIN,MAX	8,77	13,110	8,110
	Q1,Q3	27,39	27,40	27,39
	n	87	89	176
	Nmiss	31	20	51
Tricep Skinfold (mm) change V9 baseline	Mean	0.4	1.1	0.8
	Median	0.0	0.0	0.0
	SD	10.4	12.1	11.3
	MIN,MAX	-32,37	-26,64	-32,64
	Q1,Q3	-6,4	-6,6	-6,5
	n	86	88	174
	Nmiss	32	21	53

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Section 6. Mother Anthropometry

6.8.1 Maternal Bicep Skinfold at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Bicep Skinfold (mm) at Visit 2	Mean	27.4	27.8	27.6
	Median	25.0	26.0	25.5
	SD	10.1	10.7	10.4
	MIN,MAX	9,60	9,61	9,61
	Q1,Q3	21,32	20,33	21,32
	n	117	108	225
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.8.2 Maternal Bicep Skinfold at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Bicep Skinfold (mm) at Visit 6	Mean	26.7	28.4	27.5
	Median	26.1	25.0	26.0
	SD	10.3	12.2	11.2
	MIN,MAX	8,66	11,71	8,71
	Q1,Q3	19,33	20,34	20,33
	n	106	94	200
	Nmiss	12	15	27
Bicep Skinfold (mm) change V6 baseline	Mean	-0.9	0.0	-0.5
	Median	-1.0	0.0	-0.6
	SD	10.3	10.0	10.1
	MIN,MAX	-42,24	-21,33	-42,33
	Q1,Q3	-6,4	-5,4	-6,4
	n	105	93	198
	Nmiss	13	16	29

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DOI: 10.3310/eme03070

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Section 6. Mother Anthropometry

6.8.3 Maternal Bicep Skinfold at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Bicep Skinfold (mm) at Visit 9	Mean	27.5	29.5	28.6
	Median	24.0	26.0	25.0
	SD	12.5	16.5	14.6
	MIN,MAX	9,70	8,120	8,120
	Q1,Q3	20,32	20,34	20,34
	n	87	89	176
	Nmiss	31	20	51
Bicep Skinfold (mm) change V9 baseline	Mean	-0.1	2.0	1.0
	Median	-0.2	1.1	0.0
	SD	10.8	13.8	12.4
	MIN,MAX	-35,38	-20,76	-35,76
	Q1,Q3	-5,8	-5,7	-5,7
	n	86	88	174
	Nmiss	32	21	53

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.9.1 Maternal Subscapular Skinfold at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Subscapular Skinfold (mm) at Visit 2	Mean	35.3	34.8	35.1
	Median	34.0	33.0	34.0
	SD	11.0	11.7	11.3
	MIN,MAX	12,68	10,67	10,68
	Q1,Q3	28,41	27,40	27,40
	n	117	108	225
	Nmiss	1	1	2

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Section 6. Mother Anthropometry

6.9.2 Maternal Subscapular Skinfold at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Subscapular Skinfold (mm) at Visit 6	Mean	34.9	36.3	35.5
	Median	33.0	35.0	34.0
	SD	13.1	12.6	12.9
	MIN,MAX	6,71	5,71	5,71
	Q1,Q3	26,44	28,43	27,44
	n	105	92	197
	Nmiss	13	17	30
Subscapular Skinfold (mm) change V6 base	Mean	-0.7	1.1	0.1
	Median	-1.8	0.8	0.0
	SD	10.6	10.6	10.6
	MIN,MAX	-23,39	-23,25	-23,39
	Q1,Q3	-7,4	-5,7	-6,6
	n	104	91	195
	Nmiss	14	18	32

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Mother Anthropometry

6.9.3 Maternal Subscapular Skinfold at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Subscapular Skinfold (mm) at Visit 9	Mean	35.1	36.4	35.8
	Median	32.0	34.0	33.8
	SD	13.3	12.8	13.0
	MIN,MAX	15,83	9,80	9,83
	Q1,Q3	25,42	28,45	27,44
	n	87	89	176
	Nmiss	31	20	51
Subscapular Skinfold (mm) change V9 base	Mean	0.5	1.0	0.7
	Median	-0.5	1.0	0.0
	SD	10.5	13.2	11.9
	MIN,MAX	-20,47	-31,56	-31,56
	Q1,Q3	-6,5	-8,9	-7,7
	n	86	88	174
	Nmiss	32	21	53

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Section 6. Mother Anthropometry

6.10.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated BMI (kg/m^2) at Visit 2	Mean	37.5	37.8	37.7
	Median	36.6	37.5	37.0
	SD	5.5	4.7	5.1
	MIN,MAX	30,53	30,48	30,53
	Q1,Q3	33,41	34,41	34,41
	n	118	109	227
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is a repeat from section 2.5 in this report

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.10.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated BMI (kg/m^2) at Visit 6	Mean	40.2	40.4	40.3
	Median	39.6	39.7	39.6
	SD	5.4	4.7	5.1
	MIN,MAX	31,54	32,55	31,55
	Q1,Q3	36,43	37,43	36,43
	n	105	93	198
	Nmiss	13	16	29
Calculated BMI (kg/m^2) change V6 baseli	Mean	2.6	2.4	2.5
	Median	2.4	2.5	2.4
	SD	1.7	2.1	1.9
	MIN,MAX	-3,7	-2,12	-3,12
	Q1,Q3	2,4	1,3	1,3
	n	105	93	198
	Nmiss	13	16	29

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
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Section 6. Mother Anthropometry

6.10.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and ist change from baseline*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Calculated BMI (kg/m^2) at Visit 9	Mean	37.1	38.0	37.6
	Median	36.6	37.5	37.1
	SD	4.9	5.5	5.2
	MIN,MAX	28,52	29,61	28,61
	Q1,Q3	34,40	34,41	34,41
	n	89	87	176
	Nmiss	29	22	51
Calculated BMI (kg/m^2) change V9 baseli	Mean	0.1	0.3	0.2
	Median	0.0	-0.3	-0.0
	SD	2.2	3.7	3.0
	MIN,MAX	-5,5	-7,25	-7,25
	Q1,Q3	-1,1	-1,1	-1,1
	n	89	87	176
	Nmiss	29	22	51

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.11 Maternal body percentage fat (Edinburgh)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 1	Mean	46.21	48.56	47.51
	Median	46.00	48.50	47.45
	SD	5.17	5.01	5.17
	MIN,MAX	36.0,57.3	38.5,58.7	36.0,58.7
	Q1,Q3	42.1,49.5	45.2,51.7	44.7,50.8
	n	27	33	60
	Nmiss	5	3	8
Fat (%) Visit 6	Mean	45.55	47.44	46.63
	Median	46.80	47.60	47.10
	SD	4.69	4.71	4.75
	MIN,MAX	34.3,53.5	39.1,56.3	34.3,56.3
	Q1,Q3	42.8,47.6	43.9,51.2	42.8,50.1
	n	22	29	51
	Nmiss	10	7	17

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*This summary is only applicable to Edinburgh patients
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.11 Maternal body percentage fat (Edinburgh) (Cont.)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 9	Mean	46.78	48.49	47.74
	Median	48.10	47.60	47.85
	SD	5.00	4.80	4.91
	MIN,MAX	36.6,54.1	37.9,56.7	36.6,56.7
	Q1,Q3	42.7,49.2	44.8,53.1	44.7,51.8
	n	21	27	48
	Nmiss	11	9	20

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.12 Maternal Body fat mass (Edinburgh)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 1	Mean	46.684	52.117	49.672
	Median	46.260	52.569	49.378
	SD	9.209	12.214	11.212
	MIN,MAX	31.05,72.84	28.30,76.17	28.30,76.17
	Q1,Q3	42.45,52.44	42.32,61.25	42.39,56.81
	n	27	33	60
	Nmiss	5	3	8
FatMass (kg) Visit 6	Mean	48.983	54.150	51.921
	Median	49.642	54.452	50.430
	SD	8.073	12.325	10.914
	MIN,MAX	27.38,61.62	30.52,76.38	27.38,76.38
	Q1,Q3	47.52,54.42	46.75,65.08	46.78,57.24
	n	22	29	51
	Nmiss	10	7	17

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*This summary is only applicable to Edinburgh patients
#Data have been checked, innacuracies happened at time and point
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Section 6. Mother Anthropometry

6.12 Maternal Body fat mass (Edinburgh) (Cont.)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 9	Mean	48.390	50.474	49.562
	Median	50.731	48.980	50.128
	SD	9.522	13.385	11.780
	MIN,MAX	26.64,63.25	13.56,75.76	13.56,75.76
	Q1,Q3	43.26,55.43	45.45,59.07	45.27,55.88
	n	21	27	48
	Nmiss	11	9	20

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.13 Maternal Body mass (Edinburgh)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BodyMass (kg) Visit 1	Mean	100.525	106.227	103.661
	Median	97.810	105.137	102.230
	SD	12.742	16.966	15.357
	MIN,MAX	74.97,127.06	73.54,140.37	73.54,140.37
	Q1,Q3	90.23,111.61	96.70,116.33	92.28,113.94
	n	27	33	60
	Nmiss	5	3	8
BodyMass (kg) Visit 6	Mean	106.923	112.954	110.352
	Median	105.156	111.208	108.272
	SD	10.713	16.881	14.727
	MIN,MAX	79.82,123.78	78.11,147.87	78.11,147.87
	Q1,Q3	100.00,116.18	104.43,121.06	102.35,118.56
	n	22	29	51
	Nmiss	10	7	17

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*This summary is only applicable to Edinburgh patients
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 6. Mother Anthropometry

6.13 Maternal Body mass (Edinburgh) (Cont.)*#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BodyMass (kg) Visit 9	Mean	102.723	107.627	105.481
	Median	102.540	106.227	104.381
	SD	13.705	16.223	15.217
	MIN,MAX	72.74,126.73	73.76,146.86	72.74,146.86
	Q1,Q3	96.36,114.25	98.65,115.30	97.22,114.78
	n	21	27	48
	Nmiss	11	9	20

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Mother Anthropometry

6.2.2.2.extra Maternal Weight at Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Weight-Visit_6 - pp	111.358	0.8478	106	110.983	0.8165	93	-0.375	-1.806	1.056	0.267	0.6060

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Summary statistics are presented in table 6.2.2.1 of this report
Outcome analysed using a linear regression model, ajusted by weight_V2, BMI band and centre.
Significance level set at p<0.05. Estimated mean represents the means for the Weight by allocated treatment,
SE represents standard error of the estimated means and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_6_2_2_Mother_Anthropometry_weight_v6.lst'
Parameter shown normal or near-normal behavior

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Section 7. Baby Anthropometry - All Patients

7.1.1.1 Baby Age and Weight at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Neonatal Age (days)-V8	Mean	1.34	1.12	1.24
	Median	1.00	1.00	1.00
	SD	3.00	2.63	2.82
	MIN,MAX	0.0,26.0	0.0,23.0	0.0,26.0
	Q1,Q3	0.0,2.0	0.0,1.0	0.0,1.0
	n	97	89	186
	Nmiss	21	20	41
Baby Weight* (g)-V8	Mean	3532.66	3492.74	3514.12
	Median	3575.00	3480.00	3528.00
	SD	602.66	578.47	590.27
	MIN,MAX	400.0,5060.0	2110.0,4900.0	400.0,5060.0
	Q1,Q3	3140.0,3870.0	3075.0,3880.0	3110.0,3880.0
	n	98	85	183
	Nmiss	20	24	44

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*this is the recorded weight, done for a second time and it is different from the one presented in table 4.1.1.2.2.1

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Baby Anthropometry - All Patients

7.1.1.2 Baby Lenght and Ponderal Index at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Length (cm)-V8	Mean	51.44	50.48	50.99
	Median	52.00	51.00	51.25
	SD	3.03	6.47	4.97
	MIN,MAX	43.0,63.5	0.0,61.0	0.0,63.5
	Q1,Q3	50.0,53.0	49.0,53.0	49.0,53.0
	n	94	84	178
	Nmiss	24	25	49
Baby ponderal index* -V8	Mean	2.64	2.63	2.64
	Median	2.54	2.60	2.57
	SD	0.42	0.46	0.43
	MIN,MAX	1.7,3.9	1.7,3.8	1.7,3.9
	Q1,Q3	2.4,2.9	2.3,2.9	2.4,2.9
	n	90	79	169
	Nmiss	28	30	58

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.1.3 Baby Head Circumference and Skinfold Triceps at Visit 8 (Delivery)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Head Circumfe (cm)-V8	Mean	35.32	34.88	35.11
	Median	35.00	35.00	35.00
	SD	1.78	4.54	3.38
	MIN,MAX	32.0,41.5	0.0,53.0	0.0,53.0
	Q1,Q3	34.0,36.3	34.0,36.0	34.0,36.0
	n	99	89	188
	Nmiss	19	20	39
Baby Skinfold Triceps (mm)-V8	Mean	16.26	17.29	16.76
	Median	7.00	7.00	7.00
	SD	22.04	30.05	26.14
	MIN,MAX	0.0,90.0	0.0,162.0	0.0,162.0
	Q1,Q3	5.5,11.0	5.2,10.0	5.5,10.0
	n	79	74	153
	Nmiss	39	35	74

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.1.4 Baby Skinfold Subscapular and fat at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Skinfold Subscapular (mm)- V8	Mean	14.84	15.88	15.33
	Median	7.00	6.50	7.00
	SD	21.08	29.49	25.36
	MIN,MAX	0.0,100.0	0.0,158.0	0.0,158.0
	Q1,Q3	5.0,11.0	5.4,9.0	5.0,10.0
	n	80	73	153
	Nmiss	38	36	74
BABY_FAT* (%)-V8	Mean	13.45	12.78	13.07
	Median	13.50	12.30	12.30
	SD	5.78	4.56	5.05
	MIN,MAX	2.1,24.3	5.7,20.6	2.1,24.3
	Q1,Q3	8.8,17.7	8.8,16.4	8.8,17.1
	n	15	20	35
	Nmiss	103	89	192

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.1.5 Baby Fat Mass and Body mass at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
BABY_FatMass* (kg)-V8	Mean	0.49107	0.44587	0.46524
	Median	0.43600	0.43775	0.43600
	SD	0.25963	0.19978	0.22489
	MIN,MAX	0.0583,0.9767	0.1421,0.7902	0.0583,0.9767
	Q1,Q3	0.2703,0.6536	0.2772,0.6041	0.2703,0.6186
	n	15	20	35
	Nmiss	103	89	192
BABY_BodyMass* (kg)-V8	Mean	3.49751	3.37595	3.42805
	Median	3.41780	3.44520	3.42610
	SD	0.50496	0.42194	0.45630
	MIN,MAX	2.7571,4.4472	2.5026,3.9902	2.5026,4.4472
	Q1,Q3	3.0992,3.8997	3.0842,3.7430	3.0992,3.7448
	n	15	20	35
	Nmiss	103	89	192

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat Mass and Body Mass was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Baby Anthropometry - All Patients

7.1.2.1 Baby Age and Weight at Visit 9 (Final 3 months postnatal)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Neonatal Age (days)-V9	Mean	99.95	96.84	98.40
	Median	97.00	93.50	95.00
	SD	11.91	13.87	12.98
	MIN,MAX	59.0,143.0	53.0,172.0	53.0,172.0
	Q1,Q3	92.0,105.0	91.0,101.0	92.0,103.0
	n	91	90	181
	Nmiss	27	19	46
Baby Weight (g)-V9	Mean	6075.67	6108.76	6092.31
	Median	6265.00	6111.60	6200.00
	SD	1362.04	1664.00	1517.23
	MIN,MAX	666.0,8727.0	524.0,12500	524.0,12500
	Q1,Q3	5606.0,6890.0	5433.0,6900.0	5564.0,6890.0
	n	90	91	181
	Nmiss	28	18	46

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.2.2 Baby Lenght and Ponderal Index at Visit 9 (Final 3 months postnatal)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Length (cm)-V9	Mean	68.44	61.51	64.97
	Median	62.45	62.10	62.25
	SD	57.33	7.15	40.88
	MIN,MAX	42.1,605.0	5.7,74.0	5.7,605.0
	Q1,Q3	60.1,64.5	60.7,64.0	60.4,64.0
	n	90	90	180
	Nmiss	28	19	47
Baby ponderal index* -V9	Mean	2.48	39.04	20.86
	Median	2.53	2.57	2.55
	SD	0.62	345.79	245.20
	MIN,MAX	0.0,3.7	0.3,3283.1	0.0,3283.1
	Q1,Q3	2.3,2.8	2.3,2.8	2.3,2.8
	n	89	90	179
	Nmiss	29	19	48

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - All Patients

7.1.2.3 Baby Head Circumference and Skinfold Triceps at Visit 9 (Final 3 months postnatal)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Head Circumfe (cm)-V9	Mean	41.08	41.11	41.09
	Median	41.00	41.50	41.00
	SD	1.95	5.07	3.82
	MIN,MAX	34.8,46.0	4.0,62.0	4.0,62.0
	Q1,Q3	40.0,42.0	40.0,42.4	40.0,42.2
	n	89	88	177
	Nmiss	29	21	50
BabySkinfoldTriceps (mm)-V9	Mean	23.98	25.67	24.82
	Median	11.00	11.00	11.00
	SD	35.62	35.98	35.70
	MIN,MAX	0.7,160.2	0.8,170.2	0.7,170.2
	Q1,Q3	9.0,16.0	9.0,15.2	9.0,15.2
	n	83	83	166
	Nmiss	35	26	61

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
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Section 7. Baby Anthropometry - All Patients

7.1.2.4 Baby Skinfold Subscapular and fat at Visit 9 (Final 3 months postnatal)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
BabySkinfoldSubscapular (mm)-V9	Mean	17.80	24.70	21.27
	Median	8.65	10.00	9.20
	SD	25.09	33.06	29.49
	MIN,MAX	0.5,106.0	0.7,162.0	0.5,162.0
	Q1,Q3	7.0,11.0	8.0,18.0	7.0,13.0
	n	82	83	165
	Nmiss	36	26	62
BABY_FAT* (%)-V9	Mean	25.80	23.33	24.46
	Median	25.75	23.55	23.90
	SD	5.94	5.66	5.86
	MIN,MAX	15.1,41.6	12.1,32.3	12.1,41.6
	Q1,Q3	22.2,29.0	19.6,27.8	20.6,28.8
	n	22	26	48
	Nmiss	96	83	179

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Baby Anthropometry - All Patients

7.1.2.5 Baby Fat Mass and Body mass at Visit 9 (Final 3 months postnatal)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
BABY_FatMass* (kg)-V9	Mean	1.61385	1.43933	1.51932
	Median	1.68260	1.44345	1.53335
	SD	0.44937	0.49073	0.47544
	MIN,MAX	0.8625,2.6138	0.6259,2.4550	0.6259,2.6138
	Q1,Q3	1.1920,1.9387	1.0391,1.7338	1.1096,1.8044
	n	22	26	48
	Nmiss	96	83	179
BABY_BodyMass* (kg)-V9	Mean	6.24116	6.07335	6.15190
	Median	6.30410	6.11160	6.21560
	SD	0.82294	0.92984	0.87603
	MIN,MAX	4.8014,7.7721	4.4105,8.0110	4.4105,8.0110
	Q1,Q3	5.6061,6.7473	5.3395,6.6500	5.5427,6.7473
	n	22	25	47
	Nmiss	96	84	180

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat Mass and Body Mass was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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DOI: 10.3310/eme03070

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.1 Baby Age and Weight at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Neonatal Age (days)-V8	Mean	1.34	1.12	1.24
	Median	1.00	1.00	1.00
	SD	3.00	2.63	2.82
	MIN,MAX	0.0,26.0	0.0,23.0	0.0,26.0
	Q1,Q3	0.0,2.0	0.0,1.0	0.0,1.0
	n	97	89	186
	Nmiss	20	19	39
Baby Weight* (g)-V8	Mean	3564.96	3492.74	3531.23
	Median	3580.00	3480.00	3530.00
	SD	513.52	578.47	544.49
	MIN,MAX	2400.0,5060.0	2110.0,4900.0	2110.0,5060.0
	Q1,Q3	3175.0,3870.0	3075.0,3880.0	3120.0,3880.0
	n	97	85	182
	Nmiss	20	23	43

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*this is the recorded weight, done for a second time and it is different from the one presented in table 4.1.1.2.2.1

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Baby Anthropometry - Only Alive Births

7.2.1.2.1 Baby Lenght and Ponderal Index at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Length (cm)-V8	Mean	51.44	50.48	50.99
	Median	52.00	51.00	51.25
	SD	3.03	6.47	4.97
	MIN,MAX	43.0,63.5	0.0,61.0	0.0,63.5
	Q1,Q3	50.0,53.0	49.0,53.0	49.0,53.0
	n	94	84	178
	Nmiss	23	24	47
Baby ponderal index* -V8	Mean	2.64	2.63	2.64
	Median	2.54	2.60	2.57
	SD	0.42	0.46	0.43
	MIN,MAX	1.7,3.9	1.7,3.8	1.7,3.9
	Q1,Q3	2.4,2.9	2.3,2.9	2.4,2.9
	n	90	79	169
	Nmiss	27	29	56

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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DOI: 10.3310/eme03070

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.2.2 Ponderal index #,$ - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
baby_ponderal_alive_log - pp	0.969	0.0245	90	0.973	0.0253	79	0.004	-0.040	0.048	0.038	0.8460

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Summary statistics are presented in table 7.2.1.2.1 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05. Estimated mean represents the mean of the log transformed variable by allocated treatment,Parameter shown normal or near-normal behavior
SE represents standard error of the estimated log transformed mean and N represents number of observations
*Represents the difference between the estimated log means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_7_2_2_Baby_Ponderal_delivery.lst'
#Ponderal index was calculated using the following formula: (100*(baby_weight_in_g))/((baby_lenght_in_cm)^3),
$Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.3 Baby Head Circumference and Skinfold Triceps at Visit 8 (Delivery)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Head Circumfe (cm)-V8	Mean	35.32	34.88	35.11
	Median	35.00	35.00	35.00
	SD	1.78	4.54	3.38
	MIN,MAX	32.0,41.5	0.0,53.0	0.0,53.0
	Q1,Q3	34.0,36.3	34.0,36.0	34.0,36.0
	n	99	89	188
	Nmiss	18	19	37
Baby Skinfold Triceps (mm)-V8	Mean	16.26	17.29	16.76
	Median	7.00	7.00	7.00
	SD	22.04	30.05	26.14
	MIN,MAX	0.0,90.0	0.0,162.0	0.0,162.0
	Q1,Q3	5.5,11.0	5.2,10.0	5.5,10.0
	n	79	74	153
	Nmiss	38	34	72

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.4 Baby Skinfold Subscapular and fat at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Skinfold Subscapular (mm)- V8	Mean	14.84	15.88	15.33
	Median	7.00	6.50	7.00
	SD	21.08	29.49	25.36
	MIN,MAX	0.0,100.0	0.0,158.0	0.0,158.0
	Q1,Q3	5.0,11.0	5.4,9.0	5.0,10.0
	n	80	73	153
	Nmiss	37	35	72
BABY_FAT* (%)-V8	Mean	13.45	12.78	13.07
	Median	13.50	12.30	12.30
	SD	5.78	4.56	5.05
	MIN,MAX	2.1,24.3	5.7,20.6	2.1,24.3
	Q1,Q3	8.8,17.7	8.8,16.4	8.8,17.1
	n	15	20	35
	Nmiss	102	88	190

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.1.5 Baby Fat Mass and Body mass at Visit 8 (Delivery)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
BABY_FatMass* (kg)-V8	Mean	0.49107	0.44587	0.46524
	Median	0.43600	0.43775	0.43600
	SD	0.25963	0.19978	0.22489
	MIN,MAX	0.0583,0.9767	0.1421,0.7902	0.0583,0.9767
	Q1,Q3	0.2703,0.6536	0.2772,0.6041	0.2703,0.6186
	n	15	20	35
	Nmiss	102	88	190
BABY_BodyMass* (kg)-V8	Mean	3.49751	3.37595	3.42805
	Median	3.41780	3.44520	3.42610
	SD	0.50496	0.42194	0.45630
	MIN,MAX	2.7571,4.4472	2.5026,3.9902	2.5026,4.4472
	Q1,Q3	3.0992,3.8997	3.0842,3.7430	3.0992,3.7448
	n	15	20	35
	Nmiss	102	88	190

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat Mass and Body Mass was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.1 Baby Age and Weight at Visit 9 (Final 3 months postnatal)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Neonatal Age (days)-V9	Mean	99.95	96.84	98.40
	Median	97.00	93.50	95.00
	SD	11.91	13.87	12.98
	MIN,MAX	59.0,143.0	53.0,172.0	53.0,172.0
	Q1,Q3	92.0,105.0	91.0,101.0	92.0,103.0
	n	91	90	181
	Nmiss	26	18	44
Baby Weight (g)-V9	Mean	6075.67	6108.76	6092.31
	Median	6265.00	6111.60	6200.00
	SD	1362.04	1664.00	1517.23
	MIN,MAX	666.0,8727.0	524.0,12500	524.0,12500
	Q1,Q3	5606.0,6890.0	5433.0,6900.0	5564.0,6890.0
	n	90	91	181
	Nmiss	26	16	42

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.2 Baby Lenght and Ponderal Index at Visit 9 (Final 3 months postnatal)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Length (cm)-V9	Mean	68.44	61.51	64.97
	Median	62.45	62.10	62.25
	SD	57.33	7.15	40.88
	MIN,MAX	42.1,605.0	5.7,74.0	5.7,605.0
	Q1,Q3	60.1,64.5	60.7,64.0	60.4,64.0
	n	90	90	180
	Nmiss	26	17	43
Baby ponderal index* -V9	Mean	2.48	39.04	20.86
	Median	2.53	2.57	2.55
	SD	0.62	345.79	245.20
	MIN,MAX	0.0,3.7	0.3,3283.1	0.0,3283.1
	Q1,Q3	2.3,2.8	2.3,2.8	2.3,2.8
	n	89	90	179
	Nmiss	27	17	44

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.3 Baby Head Circumference and Skinfold Triceps at Visit 9 (Final 3 months postnatal)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Head Circumfe (cm)-V9	Mean	41.08	41.11	41.09
	Median	41.00	41.50	41.00
	SD	1.95	5.07	3.82
	MIN,MAX	34.8,46.0	4.0,62.0	4.0,62.0
	Q1,Q3	40.0,42.0	40.0,42.4	40.0,42.2
	n	89	88	177
	Nmiss	27	19	46
BabySkinfoldTriceps (mm)-V9	Mean	23.98	25.67	24.82
	Median	11.00	11.00	11.00
	SD	35.62	35.98	35.70
	MIN,MAX	0.7,160.2	0.8,170.2	0.7,170.2
	Q1,Q3	9.0,16.0	9.0,15.2	9.0,15.2
	n	83	83	166
	Nmiss	33	24	57

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.4 Baby Skinfold Subscapular and fat at Visit 9 (Final 3 months postnatal)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
BabySkinfoldSubscapular (mm)-V9	Mean	17.80	24.70	21.27
	Median	8.65	10.00	9.20
	SD	25.09	33.06	29.49
	MIN,MAX	0.5,106.0	0.7,162.0	0.5,162.0
	Q1,Q3	7.0,11.0	8.0,18.0	7.0,13.0
	n	82	83	165
	Nmiss	34	24	58
BABY_FAT* (%)-V9	Mean	25.80	23.33	24.46
	Median	25.75	23.55	23.90
	SD	5.94	5.66	5.86
	MIN,MAX	15.1,41.6	12.1,32.3	12.1,41.6
	Q1,Q3	22.2,29.0	19.6,27.8	20.6,28.8
	n	22	26	48
	Nmiss	94	81	175

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.2.5 Baby Fat Mass and Body mass at Visit 9 (Final 3 months postnatal)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
BABY_FatMass* (kg)-V9	Mean	1.61385	1.43933	1.51932
	Median	1.68260	1.44345	1.53335
	SD	0.44937	0.49073	0.47544
	MIN,MAX	0.8625,2.6138	0.6259,2.4550	0.6259,2.6138
	Q1,Q3	1.1920,1.9387	1.0391,1.7338	1.1096,1.8044
	n	22	26	48
	Nmiss	94	81	175
BABY_BodyMass* (kg)-V9	Mean	6.24116	6.07335	6.15190
	Median	6.30410	6.11160	6.21560
	SD	0.82294	0.92984	0.87603
	MIN,MAX	4.8014,7.7721	4.4105,8.0110	4.4105,8.0110
	Q1,Q3	5.6061,6.7473	5.3395,6.6500	5.5427,6.7473
	n	22	25	47
	Nmiss	94	82	176

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat Mass and Body Mass was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Baby Anthropometry - Only Alive Births

7.2.3 Baby Ponderal Index at Visit 8 (Delivery) and Visit 9 (Final 3 months postnatal)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby ponderal index* -V8	Mean	2.64	2.63	2.64
	Median	2.54	2.60	2.57
	SD	0.42	0.46	0.43
	MIN,MAX	1.7,3.9	1.7,3.8	1.7,3.9
	Q1,Q3	2.4,2.9	2.3,2.9	2.4,2.9
	n	90	79	169
	Nmiss	27	29	56
Baby ponderal index* -V9	Mean	2.48	2.59	2.54
	Median	2.53	2.56	2.54
	SD	0.62	1.05	0.86
	MIN,MAX	0.0,3.7	0.3,9.8	0.0,9.8
	Q1,Q3	2.3,2.8	2.3,2.8	2.3,2.8
	n	89	89	178
	Nmiss	27	18	45

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47 By: Aryelly Rodriguez - ECTU Statistician
N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

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Section 7. Baby Anthropometry - Only Alive Births

7.2.4 Baby Weight at Visit 8 (Delivery) and Visit 9 (Final 3 months postnatal)#

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Weight* (g)-V8	Mean	3564.96	3492.74	3531.23
	Median	3580.00	3480.00	3530.00
	SD	513.52	578.47	544.49
	MIN,MAX	2400.0,5060.0	2110.0,4900.0	2110.0,5060.0
	Q1,Q3	3175.0,3870.0	3075.0,3880.0	3120.0,3880.0
	n	97	85	182
	Nmiss	20	23	43
Baby Weight (g)-V9	Mean	6075.67	6108.76	6092.31
	Median	6265.00	6111.60	6200.00
	SD	1362.04	1664.00	1517.23
	MIN,MAX	666.0,8727.0	524.0,12500	524.0,12500
	Q1,Q3	5606.0,6890.0	5433.0,6900.0	5564.0,6890.0
	n	90	91	181
	Nmiss	26	16	42

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*this is the recorded weight, done for a second time and it is different from the one presented in table 4.1.1.2.2.1

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

Section 7. Baby Anthropometry - Only Alive Births

7.2.5 Baby Lenght at Visit 8 (Delivery) and Visit 9 (Final 3 months postnatal)*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Baby Length (cm)-V8	Mean	51.44	51.09	51.28
	Median	52.00	51.00	51.50
	SD	3.03	3.31	3.16
	MIN,MAX	43.0,63.5	43.0,61.0	43.0,63.5
	Q1,Q3	50.0,53.0	49.0,53.0	49.0,53.0
	n	94	83	177
	Nmiss	23	25	48
Baby Length (cm)-V9	Mean	62.41	61.51	61.96
	Median	62.40	62.10	62.20
	SD	3.92	7.15	5.78
	MIN,MAX	42.1,73.0	5.7,74.0	5.7,74.0
	Q1,Q3	60.1,64.3	60.7,64.0	60.2,64.0
	n	89	90	179
	Nmiss	27	17	44

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.1 CRP - Visit 3 Randomisation (10-16 Weeks) and Visit 5 (28 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
CRP - V3 (mg/L)	Mean	11.41	10.04	10.75
	Median	9.05	9.00	9.00
	SD	7.94	6.30	7.21
	MIN,MAX	1.0,49.0	1.0,34.0	1.0,49.0
	Q1,Q3	5.0,15.5	5.0,14.0	5.0,15.0
	n	118	109	227
	Nmiss	0	0	0
CRP - V5 (mg/L)	Mean	10.55	9.56	10.07
	Median	8.00	7.65	8.00
	SD	7.56	6.76	7.19
	MIN,MAX	2.0,43.0	1.0,41.0	1.0,43.0
	Q1,Q3	5.0,14.0	5.0,12.0	5.0,13.0
	n	115	106	221
	Nmiss	3	3	6

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.1 CRP - Visit 6 (36 Weeks) (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
CRP - V6 (mg/L)	Mean	8.91	7.48	8.23
	Median	6.80	6.00	6.00
	SD	6.39	4.58	5.64
	MIN,MAX	1.0,43.3	1.4,29.0	1.0,43.3
	Q1,Q3	5.0,12.0	5.0,9.8	5.0,10.8
	n	104	93	197
	Nmiss	14	16	30

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.1 Total Cholesterol - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Total Cholesterol - V3 (mmol/L)	Mean	4.86	4.82	4.84
	Median	5.00	4.90	4.90
	SD	1.16	1.13	1.15
	MIN,MAX	2.1,8.3	2.2,8.2	2.1,8.3
	Q1,Q3	4.0,5.7	4.1,5.5	4.0,5.6
	n	117	108	225
	Nmiss	1	1	2
Total Cholesterol - V6 (mmol/L)	Mean	6.29	6.16	6.23
	Median	6.40	6.40	6.40
	SD	1.54	1.88	1.71
	MIN,MAX	2.5,10.5	2.6,12.7	2.5,12.7
	Q1,Q3	5.6,7.2	5.1,7.3	5.2,7.2
	n	100	91	191
	Nmiss	18	18	36

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.2 HDL - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
HDL - V3 (mmol/L)	Mean	1.67	1.64	1.65
	Median	1.60	1.60	1.60
	SD	0.38	0.39	0.39
	MIN,MAX	0.9,3.6	0.0,3.2	0.0,3.6
	Q1,Q3	1.4,1.9	1.4,1.9	1.4,1.9
	n	117	108	225
	Nmiss	1	1	2
HDL - V6 (mmol/L)	Mean	1.71	1.76	1.73
	Median	1.70	1.70	1.70
	SD	0.37	0.38	0.38
	MIN,MAX	0.9,2.9	0.9,2.7	0.9,2.9
	Q1,Q3	1.4,1.9	1.5,2.0	1.5,2.0
	n	100	91	191
	Nmiss	18	18	36

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.3 LDL - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
LDL - V3 (mmol/L)	Mean	2.98	2.90	2.94
	Median	2.90	2.84	2.90
	SD	0.75	0.90	0.83
	MIN,MAX	1.6,5.1	0.0,6.0	0.0,6.0
	Q1,Q3	2.5,3.5	2.3,3.4	2.4,3.4
	n	106	101	207
	Nmiss	12	8	20
LDL - V6 (mmol/L)	Mean	3.67	3.71	3.69
	Median	3.60	3.55	3.60
	SD	1.09	1.22	1.15
	MIN,MAX	1.1,6.8	1.8,9.2	1.1,9.2
	Q1,Q3	3.0,4.4	2.8,4.4	2.9,4.4
	n	89	80	169
	Nmiss	29	29	58

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.2.4 Triglycerides - Visit 3 Randomisation (10-16 Weeks) and Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Triglycerides - V3 (mmol/L)	Mean	1.51	1.45	1.48
	Median	1.41	1.30	1.40
	SD	0.54	0.58	0.56
	MIN,MAX	0.5,3.6	0.5,3.7	0.5,3.7
	Q1,Q3	1.1,1.8	1.1,1.6	1.1,1.7
	n	117	108	225
	Nmiss	1	1	2
Triglycerides - V6 (mmol/L)	Mean	2.79	2.84	2.81
	Median	2.70	2.69	2.70
	SD	0.90	0.96	0.93
	MIN,MAX	0.9,5.8	1.3,6.7	0.9,6.7
	Q1,Q3	2.1,3.3	2.2,3.3	2.1,3.3
	n	101	92	193
	Nmiss	17	17	34

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 8. Maternal inflammatory and metabolic variables (Secondary Outcome)

8.3 CRP, Cholesterol, HDL, LDL and Triglycerides - Visit 6 (36 Weeks) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
CRP_log_Visit6 - pp	1.962	0.1008	104	1.858	0.0963	93	-0.104	-0.275	0.067	1.433	0.2329
Cholesterol_log_Visit6 - pp	1.794	0.0379	100	1.768	0.0360	91	-0.026	-0.091	0.038	0.645	0.4230
HDL_Visit6# - pp	1.767	0.0590	100	1.822	0.0561	91	0.055	-0.046	0.155	1.142	0.2866
LDL_log_Visit6$ - pp	1.208	0.0560	89	1.221	0.0527	80	0.013	-0.081	0.107	0.079	0.7793
Triglycerides_log_Visit6 - pp	0.947	0.0525	101	0.977	0.0500	92	0.030	-0.059	0.120	0.441	0.5073

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Summary statistics are presented in tables 8.1 to 8.2 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted mean of the non-transformed or log transformed variable by allocated treatment,
SE represents standard error of the estimated means or log transfomed means and N represents number of observations
*Represents the difference between the estimated means or log transfomed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_4_other_labs_analysis_v6.lst'
#NOTE:HDL was not log transformed for the analysis
$NOTE:LDL has a value of 0 for patient 16052, this values was set to missing in the log transformation of the parameter
All parameters shown normal or near-normal behavior

Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.1 Glucose and Insuling in the umbilical cord - Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Glucose Cord - V8 (mmol/L)	Mean	3.94	4.02	3.97
	Median	3.65	3.80	3.80
	SD	1.25	1.05	1.16
	MIN,MAX	1.9,7.6	1.6,6.3	1.6,7.6
	Q1,Q3	3.0,4.6	3.1,4.9	3.1,4.8
	n	62	54	116
	Nmiss	56	55	111
Insulin Cord - V8 (mIU/ml)	Mean	11.14	12.04	11.63
	Median	9.91	10.57	10.03
	SD	7.48	9.21	8.44
	MIN,MAX	2.0,32.7	2.0,42.9	2.0,42.9
	Q1,Q3	6.4,14.3	5.2,17.0	5.5,16.3
	n	37	45	82
	Nmiss	81	64	145

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.2 HOMA-IR AND CRP in the umbilical cord - Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
HOMA-IR Cord - V8 (mIU/ml)	Mean	1.83	1.93	1.88
	Median	1.81	1.50	1.62
	SD	1.36	2.19	1.80
	MIN,MAX	0.3,6.7	0.2,12.0	0.2,12.0
	Q1,Q3	0.8,2.3	0.6,2.7	0.6,2.4
	n	32	30	62
	Nmiss	86	79	165
CRP - V8 (mmol/L)	Mean	4.85	2.15	3.60
	Median	1.00	1.00	1.00
	SD	21.89	1.82	16.11
	MIN,MAX	0.3,173.8	0.2,5.0	0.2,173.8
	Q1,Q3	1.0,5.0	1.0,5.0	1.0,5.0
	n	62	53	115
	Nmiss	56	56	112

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.3 Glucose, Insuling and HOMA-IR in the umbilical cord - Visit 8 (Delivery) - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
Glucose_cord_log_Visit_8* - pp	1.262	0.0592	62	1.322	0.0552	54	0.060	-0.046	0.166	1.269	0.2626
Insulin_cord_log_Visit_8* - pp	2.042	0.1885	37	2.170	0.1705	45	0.129	-0.217	0.475	0.551	0.4602
HOMA_cord_log_Visit_8* - pp	0.151	0.1999	32	0.215	0.1823	30	0.064	-0.328	0.457	0.108	0.7436

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Summary statistics are presented in tables 9.1 to 9.2 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and centre. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between the estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_9_1_Neonatal_cord_blood.lst'
All parameters shown normal or near-normal behavior

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Section 9. Neonatal cord blood and placenta (Secondary Outcome)

9.4 CRP in the umbilical cord - Visit 8 (Delivery)* - Statistical Analysis - POST-HOC

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Parameter(s)	*Studied effects*	*P-value Wilcoxon Test (Two-sided)*	*P-value Wilcoxon t Approx (Two-sided)*	*P-value Kruskal-Wallis Test*
CRP_CORD_VISIT_8_pp	Non_parametric_test_metformin_vs_placebo*	0.7987	0.7992	0.7987

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Summary statistics are presented in table 9.2 of this report

*This variable was non-normal and the lack of normality could not be corrected. Therefore Non-parametric testing results are presented. Significance level set at p<0.05

Calculations and detailed analysis are presented in study file 'Empowar_9_1_Neonatal_cord_blood.lst'

Section 10. Adverse Outcome

10.1.1 Maternal Complications - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any SAE (n)#	Yes	22 (18.6)	19 (17.4)	41 (18.1)
	No	96 (81.4)	90 (82.6)	186 (81.9)
Any Hypertension (n)	Yes	11 (9.3)	11 (10.1)	22 (9.7)
	No	107 (90.7)	98 (89.9)	205 (90.3)
Any Preeclampsia (n)	Yes	3 (2.5)	3 (2.8)	6 (2.6)
	No	115 (97.5)	106 (97.2)	221 (97.4)
Any Eclampsia (n)	Yes	0	1 (0.9)	1 (0.4)
	No	118 (100)	108 (99.1)	226 (99.6)
Any MembraneRupture (n)	Yes	0	2 (1.8)	2 (0.9)
	No	118 (100)	107 (98.2)	225 (99.1)

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N = number of patients randomised, n = number of observations

#This value comes from the 'CRF - Complications' and it is different from the value presented in 13.1.1.1 that comes from 'SAE form'

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Section 10. Adverse Outcome

10.1.1 Maternal Complications - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any PretermLabour (n)#	Yes	2 (1.7)	6 (5.5)	8 (3.5)
	No	116 (98.3)	103 (94.5)	219 (96.5)
Any Haemorrhage (n)	Yes	4 (3.4)	4 (3.7)	8 (3.5)
	No	114 (96.6)	105 (96.3)	219 (96.5)
Any DVT (n)	Yes	2 (1.7)	0	2 (0.9)
	No	116 (98.3)	109 (100)	225 (99.1)
Any Gestational Diabetes (n)	Yes	19 (16.1)	14 (12.8)	33 (14.5)
	No	99 (83.9)	95 (87.2)	194 (85.5)

N = number of patients randomised, n = number of observations

#This value comes from the 'CRF - Complications' and it is different from the value presented in 4.1.1.1 that comes from 'CRF - delivery'

Section 10. Adverse Outcome

10.1.1 Maternal Complications - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Other Mother Complication (n)	Yes	37 (31.4)	44 (40.4)	81 (35.7)
	No	81 (68.6)	65 (59.6)	146 (64.3)
Any Other Mother Complication cat* (n)	Missing	0	1	1
	Infection	10	12	22
	Mood disturbance	1	4	5
	Musculoskeletal	8	14	22
	PV bleed <24 weeks gestation	3	3	6
	Obstetric cholestasis	4	1	5
	Miscellaneous	13	18	31
	Data captured elsewhere	28	24	52

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N = number of patients randomised, n = number of observations
*A single patient could have had more than one complication
The complications were categorised by the study team

By: Aryelly Rodriguez - ECTU Statistician

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Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
11136	METFORMIN	Yes	VISIT 8 (DELIVERY)	placental abruption
11315	METFORMIN	Yes	VISIT 8 (DELIVERY)	3rd degree tear
11325	METFORMIN	Yes	VISIT 5 (28 WEEKS)	antenatal depression
11501	METFORMIN	Yes	VISIT 6 (36 WEEKS)	hospital admission with RUQ pain and deranged LFT, resolved spontaneously
11551	METFORMIN	Yes	VISIT 5 (28 WEEKS)	exacerbation of asthma requiring oral steroids
11716	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Mild SPD
11748	METFORMIN	Yes	VISIT 6 (36 WEEKS)	UTI
11748	METFORMIN	Yes	VISIT 7 (TERM)	Sepsis secondary to mastitis
11748	METFORMIN	Yes	VISIT 8 (DELIVERY)	UTI SAE forms previously sent
11797	METFORMIN	Yes	VISIT 6 (36 WEEKS)	excessive vomiting in late pregnancy
11842	METFORMIN	Yes	VISIT 8 (DELIVERY)	Raised ALT
11881	METFORMIN	Yes	VISIT 8 (DELIVERY)	severe urosepsis
12001	METFORMIN	Yes	VISIT 7 (TERM)	Sweling of hands and feet
12001	METFORMIN	Yes	VISIT 8 (DELIVERY)	oedema
12008	METFORMIN	Yes	VISIT 8 (DELIVERY)	Post Partum haemorrhage, 2000ml
12018	METFORMIN	Yes	VISIT 8 (DELIVERY)	EBL 600 mls
13016	METFORMIN	Yes	VISIT 7 (TERM)	Seen in assessment room last week with headache and visual disturbances. Migrane diagnosed. Discharged home with paracetamol and codine.
13082	METFORMIN	Yes	VISIT 8 (DELIVERY)	PYREXIA IN LABOUR
13209	METFORMIN	Yes	VISIT 6 (36 WEEKS)	HAD VIRAL INFECTION 2 WEEKS AGO LASTING A FORTNIGHT. RESULTED IN PRODUCTIVE COUGH, FOLLOWED MODERATE VOMITTING AND DIARROHEA.
13378	METFORMIN	Yes	VISIT 5 (28 WEEKS)	UTI CAUSED SEVERE HEADACHES. CLEARED AFTER COURSE OF ANTIBIOTICS.
13378	METFORMIN	Yes	VISIT 8 (DELIVERY)	Fatty deposits noted on placenta, samples taken for histology by delivery midwife, but enable to process as incorrectly sampled and stored
13551	METFORMIN	Yes	VISIT 8 (DELIVERY)	PPH of 5000ml followed by total hysterectomy
13780	METFORMIN	Yes	VISIT 8 (DELIVERY)	UNDIAGNOSED LOW LYING PLACENTA AT CS. BLOOD LOSS 1400MLS. NEEDED BLOOD TRANSFUSION AFTER CS.
14303	METFORMIN	Yes	VISIT 8 (DELIVERY)	PPH 1200mls
14417	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Feeling faint on occasions when working
15012	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	has had small pv bleed as history of cervical polyps all well
15027	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Itching All blood tests NAD
16054	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Abdo pain and pinkish pv loss
16121	METFORMIN	Yes	VISIT 6 (36 WEEKS)	pyelonephritis
17138	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Palpitations, seen in hospital assessment unit but discharged home without admission. Normal ECG and Normal CTG.
21015	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Attended Day Unit 4/9/13 33+4 with brown pv discharge post coital.
21015	METFORMIN	Yes	VISIT 7 (TERM)	Questions asked in retrospect once delivered as unable to contact.Unsure when stopped tablets.
21015	METFORMIN	Yes	VISIT 8 (DELIVERY)	PPH following birth.Hb 63g/l.Had 2 units of blood.Hb 83g/l post transfusion.Didnt cause prolonged hospitalisation.
21034	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Indigestion since 22 weeks resolved with use of gaviscon
21034	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Acupuncture for back/hip pain. Broke coccyx 5 years ago

Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
21037	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Sweating
21037	METFORMIN	Yes	VISIT 7 (TERM)	Green vaginal discharge today High vaginal swab obtained.
21039	METFORMIN	Yes	VISIT 8 (DELIVERY)	Maternal tachycardia post delivery. IV fluids & antibiotics given. Ragged membranes.
21042	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Heartburn. Using gaviscon. Awaiting precription of ranitidine
21042	METFORMIN	Yes	VISIT 5 (28 WEEKS)	07/09/2013 self referral to maty ward feeling dizzy. 21/09/2013 ?SROM HVS showed Group B Strep. On last day of Amoxycillin treatment today.Gestational diabetes today. Attending for glucometer tomorrow
21042	METFORMIN	Yes	VISIT 7 (TERM)	Group B Strep diagnosed in pregnancy.
21042	METFORMIN	Yes	VISIT 8 (DELIVERY)	Induction of labour for gestational diabetes. Group B Strep identified in pregnancy.
21064	METFORMIN	Yes	VISIT 5 (28 WEEKS)	UTI 21/10/13 cephalexin tds for 5 days taken.
21064	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Right sided abdo pain on 2 occasions 15 & 22/11/13 been fine since.
21064	METFORMIN	Yes	VISIT 8 (DELIVERY)	SPD
21070	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Lower backache has appt with physio on 8/10/13
21070	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Symphisis Pubis Disfunction-physio input
21070	METFORMIN	Yes	VISIT 6 (36 WEEKS)	SPD
21070	METFORMIN	Yes	VISIT 8 (DELIVERY)	SPD-S/B Physio & had acupuncture.
21074	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Backache 16+ weeks saw GP & resolved a few days later
21074	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Wort on finger.
21074	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Itching on legs, had same prior to pregnancy. Wort on finger.
21074	METFORMIN	Yes	VISIT 7 (TERM)	03/02/14 headache for 24 hours.Started on antibiotics as ?UTI. Normal MSSU so stopped taking. Only took 1 tablet.
21074	METFORMIN	Yes	VISIT 8 (DELIVERY)	26/2/14 perineal infection flucloycillin commenced orally at home.
21082	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	20/10/13 attended primary care/gynae feeling unwell ?food poisoning/palpatations normal investigations.Some low mood/depression.
21082	METFORMIN	Yes	VISIT 6 (36 WEEKS)	3/1/14 29+4 episode of raised BP settled. 30/1/14 33+3 antibiotics for UTI.
21082	METFORMIN	Yes	VISIT 7 (TERM)	Some hypertension-settled now.
21082	METFORMIN	Yes	VISIT 8 (DELIVERY)	Pyrexial in labour/maternal tachycardia. IV paracetamol required.
21095	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Started citalopram for depression on 04/11/13.
21095	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Lower back discomfort sees physio.
21095	METFORMIN	Yes	VISIT 8 (DELIVERY)	On citalopram for depression
21099	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Tooth abcess so had to reduce tablets one day.
21099	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Eleveated BP today for close monitoring. Occasionally takes Co-dydramol for backache. Physio/acupuncture unsucessful.
21099	METFORMIN	Yes	VISIT 8 (DELIVERY)	Raised blood pressure
21111	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Small pv bleed 08/12/13 19+ weeks. Investigations NAD. Not admitted to Gynae.
21111	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Upper abdominal discomfort for 4-5 weeks on and off.
21111	METFORMIN	Yes	VISIT 7 (TERM)	Amoxycillin 500mgs TDS for suspected chest infection.
21127	METFORMIN	Yes	VISIT 5 (28 WEEKS)	SPD on crutches seeing physio.
21127	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Seeing physio & having acupuncture for hip pain.
21127	METFORMIN	Yes	VISIT 8 (DELIVERY)	SPD/Hip pain. Has seen physio/had crutches/acupuncture.

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DOI: 10.3310/eme03070

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10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
21128	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Backache & sciatica
21128	METFORMIN	Yes	VISIT 8 (DELIVERY)	Postpartum haemorrhage.
25264	METFORMIN	Yes	VISIT 5 (28 WEEKS)	obstetric cholestasis
25382	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	diarrhoea
25459	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Right Adrexal ovarian cyst
25459	METFORMIN	Yes	VISIT 8 (DELIVERY)	Induction of labour due to pain from known ovarian cyst
53059	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Had contact with nephew with chicken pox and does not have immunity. Therefore had to attend for immunoglobulin
11081	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	on going hyperemesis requiring antiemetic (predates trial)
11323	PLACEBO	Yes	VISIT 8 (DELIVERY)	3rd degree tear (3a)
11443	PLACEBO	Yes	VISIT 6 (36 WEEKS)	itch-possible obstetric cholestasis
11693	PLACEBO	Yes	VISIT 8 (DELIVERY)	Obstetric cholestasis
11725	PLACEBO	Yes	VISIT 7 (TERM)	SPD
11940	PLACEBO	Yes	VISIT 6 (36 WEEKS)	currently on prednisolone for chest infection
11940	PLACEBO	Yes	VISIT 8 (DELIVERY)	Hospitalised due to chest infection.
12019	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Thrush
12020	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Ear infection/vertigo
12020	PLACEBO	Yes	VISIT 5 (28 WEEKS)	vertigo
12020	PLACEBO	Yes	VISIT 8 (DELIVERY)	PPH 1500 - 2500 mls
12021	PLACEBO	Yes	VISIT 5 (28 WEEKS)	25/04/2012 In triage for UTI. Sent home with trimetheprim.
12065	PLACEBO	Yes	VISIT 8 (DELIVERY)	Diet controlled GDM
13007	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Was weepy when increased dose to 4 tablets at week 4. Therefore has decreased to 2 tablets daily. Not having weepiness any longer, suggested trying to increase to TDS, - will try, but not willing to increase dose further. 4/3/11
13058	PLACEBO	Yes	VISIT 6 (36 WEEKS)	vomiting and feeling very unwell migraines increasingly worse
13144	PLACEBO	Yes	VISIT 5 (28 WEEKS)	SYMPHISIS PUBIS DISORDER
13144	PLACEBO	Yes	VISIT 7 (TERM)	Has had fainting episodes for past 6 weeks. Now has IOL booked for 38wks due to this. Reports has had several addmissions with raised blood pressure and protien urea.
13144	PLACEBO	Yes	VISIT 8 (DELIVERY)	Reported frequent fainting episodes. not investigated, occassional episodes of raised BP, BP profile NAD. IOL on request in view of repeaded fainting.
13217	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Hip pain due to looseness in joint. Under physio. Not on medication.
13217	PLACEBO	Yes	VISIT 8 (DELIVERY)	PPH, HAD OXYTOCIC DRUGS
13301	PLACEBO	Yes	VISIT 5 (28 WEEKS)	HAD COLLAPSE WHEN OUT SHOPPING. ADVISED TO STOP MEDICATION AS GLUCOSE LEVEL WAS REPORTED TO BE LOW WHEN CHECKED AT GP.
13301	PLACEBO	Yes	VISIT 8 (DELIVERY)	Intrapartum haemmorhage and postnatal haemorrhage total = 2000ml
13591	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Fell on the bus when it stopped suddenly. Had small pv bleed, attended hospital for anti d, but was not admitted and not for any follow up. As reports fall was due to bus stopping suddenly and no episodes of dizziness or feeling faint not an SAE.
13667	PLACEBO	Yes	VISIT 8 (DELIVERY)	IOL FOR SPD PPH 1200ML
13712	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Obstetric Choleostasis
13712	PLACEBO	Yes	VISIT 8 (DELIVERY)	choleostasis
14205	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Double vision. Currently under investigation by eye clinic.
14336	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Seen by SHO in Triage 13.09.13 re abdominal pain. Now resolved ?viral enteritis

Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Other Maternal Complications (Y/N)	TimepointID	Other Maternal Complications Details
14336	PLACEBO	Yes	VISIT 8 (DELIVERY)	see SAE
14354	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Ovarian cyst on right ovary diagnosed
14354	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Admitted with small APH and tightenings for 5 days - SAE completed 22.12.13
14413	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Abdominal pain 03.10.13 Seen in Early Pregnancy Assessment Centre
15010	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	metallic taste
15010	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Has some itching bile acids nad
17036	PLACEBO	Yes	VISIT 7 (TERM)	hospital admission as had flu
17036	PLACEBO	Yes	VISIT 8 (DELIVERY)	raised ALT liver scan
17137	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Costochondritis
17137	PLACEBO	Yes	VISIT 8 (DELIVERY)	Costochondritis
21010	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Persistent glycosuria between 28+ and 35+ weeks gestation. Normal GTTs.
21018	PLACEBO	Yes	VISIT 5 (28 WEEKS)	pv bleed before 16 weeks gestation, prior to commencing tablets.Hospitalised for observation discharged within 12 hours.
21018	PLACEBO	Yes	VISIT 6 (36 WEEKS)	4/9/13 32+6 shortness of breath/palpitations. Investigations normal.
21018	PLACEBO	Yes	VISIT 7 (TERM)	Various episodes of reduced fetal movements see on MDCU had CTGs. H/o palpatations normal investigations.
21018	PLACEBO	Yes	VISIT 8 (DELIVERY)	Difficult caesarean section.
21038	PLACEBO	Yes	VISIT 8 (DELIVERY)	Readmitted via ambulance 29/12/13 pv bleed/abdo pain. Stayed in hospital for less than 12 hours. No SAE required.
21044	PLACEBO	Yes	VISIT 6 (36 WEEKS)	pyogenic granuloma on finger of left hand.Had x2 doses of flucloxycillin.UTI cephalexin for 1 week.
21047	PLACEBO	Yes	VISIT 5 (28 WEEKS)	20+4 (3-4/9/13) brief episode in A&E pain from gall stones settled after morphine discharged home after few hours.
21069	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Antibiotics for 1 week for ear infection 05/09/13
21069	PLACEBO	Yes	VISIT 5 (28 WEEKS)	UTI treated with cefalexin.
21069	PLACEBO	Yes	VISIT 8 (DELIVERY)	Sepsis in labour.SAE form completed as prolonged hospitalisation.
21078	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Hb low for oral iron
21078	PLACEBO	Yes	VISIT 6 (36 WEEKS)	16/1/14 episode of reduced fetal movements. CTG NAD.
21078	PLACEBO	Yes	VISIT 7 (TERM)	On ferrous sulphate tablets as anaemic since last visit.
21093	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Small antepartum haemorrhage. Overnight stay on maternity ward for over 12 hours.
21093	PLACEBO	Yes	VISIT 6 (36 WEEKS)	28/12/13 sight pv bleeding no admission. 24/1/14 Antibiotics for bacterial vaginosis & canestan for thrush. 3/2/14 brief isolated episode of raised BP settled on day unit no admission.
21093	PLACEBO	Yes	VISIT 8 (DELIVERY)	Raised BP in labour
21109	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Heartburn. Day Unit visit 16/12/13 abdo pain.
21109	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Admitted over 12 hours with UTI. Oral antibiotics/steroids/ferrous sulphate.SAE form completed & faxed to Sponsors.
21109	PLACEBO	Yes	VISIT 7 (TERM)	Admitted for 2 nights on 03/4/14 with lower abdo discomfort, braxton hicks, red pv loss, unstable lie.
21109	PLACEBO	Yes	VISIT 8 (DELIVERY)	Admitted with lower abdo discomfort, red pv loss, Braxton Hicks,unstable lie 03/4/14
21122	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Prolonged nausea.
21122	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Prolonged nausea
21122	PLACEBO	Yes	VISIT 7 (TERM)	Musculoskeletal pain/SPD. Group B Strep positive.
21122	PLACEBO	Yes	VISIT 8 (DELIVERY)	SPD/musculoskeletal pain. Group B Strep positive.

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DOI: 10.3310/eme03070

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Section 10. Adverse Outcome

10.1.2 Maternal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*Other Maternal Complications (Y/N)*	*TimepointID*	*Other Maternal Complications Details*
25391	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	brown/green pv loss on 2.11.13. pv spotting on 12.11.13. HVS group B streptococcus.
25391	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Abdominal pain ?cause
25391	PLACEBO	Yes	VISIT 7 (TERM)	depression and musculoskeletal pain
53014	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	has had persistant cough since sept. Has seen own doctor (GP, had course of antibiotics. Also seen at general hospital advised re inhalers and improved with this (as is asthmatic)

Section 10. Adverse Outcome

10.1.3.1 Maternal Complications - Hypertension - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency

Table of ANY_HYPER by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
ANY_HYPER	*METFORMIN*	*PLACEBO*	*Total*
No	98	107	205
Yes	11	11	22
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
ANY_HYPER_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.092	0.453	2.631	0.8448	1.0000

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47

By: Aryelly Rodriguez - ECTU Statistician

*Analised using logistic regression (binary logit), probability modeled is ANY_hyper='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_10_1_1_Npatients_hypertension_analysis.lst'

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DOI: 10.3310/eme03070

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Section 10. Adverse Outcome

10.1.3.2 Maternal Complications - Preeclampsia - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery) - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of ANY_Preecla by AllocatedTreatment*

	AllocatedTreatment(Allocated Treatment)		
ANY_Preecla	*METFORMIN*	*PLACEBO*	*Total*
No	106	115	221
Yes	3	3	6
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
ANY_Preecla_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.085	0.214	5.493	0.9216	1.0000

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47

*Analised using logistic regression (binary logit), probability modeled is ANY_preecla='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_10_1_1_Npatients_preeclamp_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 10. Adverse Outcome

10.2.1 Fetal Complications* - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Fetal Complication (n)	Yes	28 (23.7)	26 (23.9)	54 (23.8)
	No	90 (76.3)	83 (76.1)	173 (76.2)
Fetal AC (n)	Missing	118	109	227
Fetal Liquor (n)	Missing	77	76	153
	Yes	2	3	5
	No	39	30	69
Fetal Doppler (n)	Missing	77	77	154
	No	41	32	73
Fetal Absent EDF (n)	Missing	78	77	155
	Yes	1	0	1
	No	39	32	71

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47
N = number of patients randomised, n = number of observations
*A single patient could have had more than one complication

By: Aryelly Rodriguez - ECTU Statistician

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Section 10. Adverse Outcome

10.2.1 Fetal Complications* - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)(Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Fetal Reverse EDF (n)	Missing	78	77	155
	No	40	32	72
Fetal Abnormal CTG (n)	Missing	77	77	154
	Yes	8	8	16
	No	33	24	57
Other Fetal Complication (n)	Missing	70	69	139
	Yes	21	21	42
	No	27	19	46
Other Fetal Complication cat#(n)	Data captured elsewhere	12	10	22
	Meconium stained liquor	3	4	7
	Miscellanous	1	1	2
	Polyhydramnios	3	3	6
	Reduced fetal movements	3	7	10
	Shoulder dystocia	2	0	2

N = number of patients randomised, n = number of observations

*A single patient could have had more than one complication

#The complications were categorised by the study team

Section 10. Adverse Outcome

10.2.2 Fetal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	Fetal Complications Other (Y/N)	TimepointID	Fetal Complications Other Details
11557	METFORMIN	Yes	VISIT 8 (DELIVERY)	reduced fetal movements and clinically felt to be small for dates although growth scan normal
12001	METFORMIN	Yes	VISIT 8 (DELIVERY)	macrosomia
12018	METFORMIN	Yes	VISIT 6 (36 WEEKS)	scan at 36 weeks shows abdominal circumstance static,attending further scan in one week
12034	METFORMIN	Yes	VISIT 8 (DELIVERY)	Premature delivery.
13551	METFORMIN	Yes	VISIT 8 (DELIVERY)	Low Cord PH's on FBS
14303	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Polyhydramnios
15003	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Breech presentation
16064	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Reduced fetal movements x 2 days
16121	METFORMIN	Yes	VISIT 7 (TERM)	Persistent reduced fetal movements
16121	METFORMIN	Yes	VISIT 8 (DELIVERY)	Persistent reduced fetal movements
16133	METFORMIN	Yes	VISIT 7 (TERM)	polyhydramnios
16133	METFORMIN	Yes	VISIT 8 (DELIVERY)	polyhydramnios
17047	METFORMIN	Yes	VISIT 8 (DELIVERY)	Meconium liquor
21042	METFORMIN	Yes	VISIT 6 (36 WEEKS)	Episodes of reduced fetal movements.
21070	METFORMIN	Yes	VISIT 8 (DELIVERY)	Thick meconium liquor on SROM.
21074	METFORMIN	Yes	VISIT 6 (36 WEEKS)	x1 episode of no fetal movements 25/11/13 28+5. Normal CTG.
21074	METFORMIN	Yes	VISIT 7 (TERM)	Reduced fetal movements 03/02/14. Normal scan.
21082	METFORMIN	Yes	VISIT 5 (28 WEEKS)	Growth below lower centile.
21082	METFORMIN	Yes	VISIT 8 (DELIVERY)	Thick meconium liquor. Fetal tachycardia in labour.
21095	METFORMIN	Yes	VISIT 8 (DELIVERY)	Meconium liquor
21127	METFORMIN	Yes	VISIT 8 (DELIVERY)	Growth on 10th centile.
21128	METFORMIN	Yes	VISIT 8 (DELIVERY)	IUGR. Growth on lower centile. Double knot in cord.
25226	METFORMIN	Yes	VISIT 8 (DELIVERY)	Baby had IVABX as prev NND for Group B Strep and EColi.
25459	METFORMIN	Yes	VISIT 4 (18 TO 20 WEEKS)	Anomoly scan show right unilateral talipes
53059	METFORMIN	Yes	VISIT 6 (36 WEEKS)	HAD 2X GROWTH USS FOR ?IUGR. SECOND USS SHOWED NORMAL GROWTH.
11386	PLACEBO	Yes	VISIT 8 (DELIVERY)	shoulder dystocia, relieved with McRoberts and suprapubic pressure, Apgars 8 and 9
11564	PLACEBO	Yes	VISIT 8 (DELIVERY)	baby required resuscitation at delivery
11632	PLACEBO	Yes	VISIT 8 (DELIVERY)	Suspected IUGR
12020	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Reduced fetal movements
12021	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Polyhydramnios
12021	PLACEBO	Yes	VISIT 6 (36 WEEKS)	po;yhydramnios detected on scan at 28+4 weeks. Large for getational age detected at 34+2 weeks.
13301	PLACEBO	Yes	VISIT 8 (DELIVERY)	Undiagnosed oblique breech lie, intrapartum haemorrhage
13473	PLACEBO	Yes	VISIT 8 (DELIVERY)	Baby admitted to NICU for low BM's for 24 hours. No IV fluids required, baby tube fed only. Lowest BM 1.7mmol. Now maintaining BM's and back on postnatal ward with mum
13591	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Raised growth on USS, at 32/40 and 35/40 measurments >95th centile. EFW at 35/40 3456g
13591	PLACEBO	Yes	VISIT 8 (DELIVERY)	Suspected fetal macrosomia
14264	PLACEBO	Yes	VISIT 8 (DELIVERY)	Intermittently absent EDF

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Section 10. Adverse Outcome

10.2.2 Fetal Complications Details - from Visit 4 (18-20 Weeks) to Visit 8 (Delivery)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	*Allocated Treatment*	*Fetal Complications Other (Y/N)*	*TimepointID*	*Fetal Complications Other Details*
15010	PLACEBO	Yes	VISIT 5 (28 WEEKS)	one episode of reduced fetal movements ctg monitoring normal
16053	PLACEBO	Yes	VISIT 8 (DELIVERY)	shoulder dystocia
18114	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Measuring Large for Dates. Head circumference and abdominal circumference above 95th centile.
21018	PLACEBO	Yes	VISIT 6 (36 WEEKS)	Polyhydramnious on uss 8/8/13 (29 weeks) & 21/8/13 (30+6 weeks) has since resolved. Reduced fetal movements had monitoring on x4 occasions & again today.
21038	PLACEBO	Yes	VISIT 5 (28 WEEKS)	Growth on lower centile today. Normal doppler
21069	PLACEBO	Yes	VISIT 8 (DELIVERY)	Thick meconium stained liquor during labour.
21093	PLACEBO	Yes	VISIT 6 (36 WEEKS)	27/1/14 growth on lower centile. 03/2/14 mild polyhyrdamnious. 10/2/14 normal growth & liquor volume.
21093	PLACEBO	Yes	VISIT 8 (DELIVERY)	Light, thin meconium liquor
21109	PLACEBO	Yes	VISIT 6 (36 WEEKS)	21/02/2014 uss normal growth. Liquor volume just above upper centile.
21119	PLACEBO	Yes	VISIT 4 (18 TO 20 WEEKS)	Fetal abnormality on anomaly ultrasound scan.
25034	PLACEBO	Yes	VISIT 8 (DELIVERY)	meconium stained liquor
25320	PLACEBO	Yes	VISIT 8 (DELIVERY)	baby's scan on the 30/1/2014 continued to show baby had a full stomach. suspected Hirschsprungs disease in neonate.
25364	PLACEBO	Yes	VISIT 7 (TERM)	Large for dates on scan

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Section 11. Neonatal Care - All Patients

11.1 Neonatal Care

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Care after delivery (n(%))	Missing	1	1	2
	Normal Care	100 (85.5)	98 (90.7)	198 (88.0)
	Special Care	6 (5.1)	4 (3.7)	10 (4.4)
	Level 2 intensive care (ie high dependency intensive care)	6 (5.1)	3 (2.8)	9 (4.0)
	Level 1 intensive care (maximal intensive care)	1 (0.9)	1 (0.9)	2 (0.9)
	Other	4 (3.4)	2 (1.9)	6 (2.7)
Any Congenital Abnormality (n(%))	Missing	2	2	4
	Yes	5 (4.3)	4 (3.7)	9 (4.0)
	No	111 (95.7)	103 (96.3)	214 (96.0)
Other Hospital Admission (n(%))	Missing	9	7	16
	Yes	2 (1.8)	1 (1.0)	3 (1.4)
	No	107 (98.2)	101 (99.0)	208 (98.6)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 11. Neonatal Care - Only Alive Births

11.2.1 Neonatal Care

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Care after delivery (n(%))	Missing	1	0	1
	Normal Care	100 (86.2)	98 (90.7)	198 (88.4)
	Special Care	6 (5.2)	4 (3.7)	10 (4.5)
	Level 2 intensive care (ie high dependency intensive care)	6 (5.2)	3 (2.8)	9 (4.0)
	Level 1 intensive care (maximal intensive care)	1 (0.9)	1 (0.9)	2 (0.9)
	Other	3 (2.6)	2 (1.9)	5 (2.2)
Any Congenital Abnormality (n(%))	Missing	2	1	3
	Yes	4 (3.5)	4 (3.7)	8 (3.6)
	No	111 (96.5)	103 (96.3)	214 (96.4)
Other Hospital Admission (n(%))	Missing	9	6	15
	Yes	2 (1.9)	1 (1.0)	3 (1.4)
	No	106 (98.1)	101 (99.0)	207 (98.6)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

Section 11. Neonatal Care - Only Alive Births

11.2.2 Neonatal care after delivery - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Care_Deliv by AllocatedTreatment*

	AllocatedTreatment(Allocated Treatment)		
Care_Deliv	*METFORMIN*	*PLACEBO*	*Total*
Missing	0	1	.
No	100	103	203
Yes	8	13	21
Total	108	116	224

Frequency Missing = 1

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
Care_Deliv_pp	AllocatedTreatment METFORMIN vs PLACEBO	0.634	0.252	1.595	0.3329	0.3667

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*Analised using logistic regression (binary logit), probability modeled is Care_Deliv='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_11_2_Neonatal_unit.lst'

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Section 11. Neonatal Care - Only Alive Births

11.2.3 Any Congenital Abnormality - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Abnormal by AllocatedTreatment*

	AllocatedTreatment(Allocated Treatment)		
Abnormal	*METFORMIN*	*PLACEBO*	*Total*
Missing	1	2	.
No	103	111	214
Yes	4	4	8
Total	107	115	222

Frequency Missing = 3

Parameter(s)	*Studied effects*		*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
Abnormal_pp	AllocatedTreatment	METFORMIN vs PLACEBO	1.078	0.263	4.421	0.9173	1.0000

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*Analised using logistic regression (binary logit), probability modeled is Abnormal='Yes'
#Significance level set at p<0.05
Detailed analysis in file 'Empowar_11_2_Neonatal_unit.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.1.1 Taste Disturbance - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Taste Disturbance (n(%))	Yes	20 (16.9)	17 (15.6)	37 (16.3)
	No	98 (83.1)	92 (84.4)	190 (83.7)
Taste Disturbance severity (n)	Mild	11	10	21
	Moderate	9	3	12
	Severe	0	4	4

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Section 12. Maternal symptoms up to 36 weeks gestation

12.1.2 Taste Disturbance - Statistical analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of TasteDis_ana by AllocatedTreatment*

TasteDis_ana(Taste disturbance at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	17	20	37
No	92	98	190
Total	109	118	227

Parameter(s)	*Studied effects*		*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
tastedis_pp	AllocatedTreatment	METFORMIN vs PLACEBO	0.905	0.447	1.835	0.7828	0.8581

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*Analised using logistic regression (binary logit), probability modeled is TasteDis_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.2.1 Skin Reaction - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Skin Reaction (n(%))	Yes	23 (19.5)	21 (19.3)	44 (19.4)
	No	95 (80.5)	88 (80.7)	183 (80.6)
Skin Reaction severity (n)	Mild	13	12	25
	Moderate	8	7	15
	Severe	2	2	4

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Section 12. Maternal symptoms up to 36 weeks gestation

12.2.2 Skin Reaction - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of SkinReac_ana by AllocatedTreatment*

SkinReac_ana(Skin Reaction at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	21	23	44
No	88	95	183
Total	109	118	227

Parameter(s)	*Studied effects*		*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
skinreac_pp	AllocatedTreatment	METFORMIN vs PLACEBO	0.986	0.510	1.905	0.9658	1.0000

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*Analised using logistic regression (binary logit), probability modeled is SkinReac_ana='Yes'

#Significance level set at p<0.05

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Section 12. Maternal symptoms up to 36 weeks gestation

12.3.1 Abdominal Pain - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Abdominal Pain (n(%))	Yes	26 (22.0)	32 (29.4)	58 (25.6)
	No	92 (78.0)	77 (70.6)	169 (74.4)
Abdominal Pain severity (n)	Mild	16	21	37
	Moderate	8	10	18
	Severe	2	1	3

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Event with the highest severity picked for summary

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Section 12. Maternal symptoms up to 36 weeks gestation

12.3.2 Abdominal Pain - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of AbdoPain_ana by AllocatedTreatment*

AbdoPain_ana(Abdominal Pain at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	32	26	58
No	77	92	169
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
abdopain_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.471	0.807	2.678	0.2074	0.2255

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*Analised using logistic regression (binary logit), probability modeled is AbdoPain_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.4.1 Flatulence - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Flatulence (n(%))	Yes	28 (23.7)	38 (34.9)	66 (29.1)
	No	90 (76.3)	71 (65.1)	161 (70.9)
Flatulence severity (n)	Mild	16	16	32
	Moderate	9	16	25
	Severe	3	6	9

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Section 12. Maternal symptoms up to 36 weeks gestation

12.4.2 Flatulence - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Flatu_ana by AllocatedTreatment*

Flatu_ana(Flatulence at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	38	28	66
No	71	90	161
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
flatu_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.720	0.964	3.069	0.0662	0.0793

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*Analised using logistic regression (binary logit), probability modeled is Flatu_ana='Yes'
#Significance level set at p<0.05
Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.5.1 Constipation - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Constipation (n(%))	Yes	38 (32.2)	37 (33.9)	75 (33.0)
	No	80 (67.8)	72 (66.1)	152 (67.0)
Constipation severity (n)	Mild	19	21	40
	Moderate	17	11	28
	Severe	2	5	7

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Section 12. Maternal symptoms up to 36 weeks gestation

12.5.2 Constipation - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Consti_ana by AllocatedTreatment*

Consti_ana(Constipation at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	37	38	75
No	72	80	152
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
consti_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.082	0.622	1.882	0.7805	0.8878

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*Analised using logistic regression (binary logit), probability modeled is Consti_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.6.1 Diarrhoea - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Diarrhoea (n(%))	Yes	24 (20.3)	60 (55.0)	84 (37.0)
	No	94 (79.7)	49 (45.0)	143 (63.0)
Diarrhoea severity (n)	Mild	14	34	48
	Moderate	8	21	29
	Severe	2	5	7

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Section 12. Maternal symptoms up to 36 weeks gestation

12.6.2 Diarrhoea - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Diarrh_ana by AllocatedTreatment*

Diarrh_ana(Diarrhoea at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	60	24	84
No	49	94	143
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
diarrh_pp	AllocatedTreatment METFORMIN vs PLACEBO	4.796	2.669	8.617	<.0001	0.0000

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*Analised using logistic regression (binary logit), probability modeled is Diarrh_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.7.1 Nausea - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Nausea (n(%))	Yes	46 (39.0)	49 (45.0)	95 (41.9)
	No	72 (61.0)	60 (55.0)	132 (58.1)
Nausea severity (n)	Mild	31	27	58
	Moderate	13	19	32
	Severe	2	3	5

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Section 12. Maternal symptoms up to 36 weeks gestation

12.7.2 Nausea - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Nausea_ana by AllocatedTreatment*

Nausea_ana(Nausea at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	49	46	95
No	60	72	132
Total	109	118	227

Parameter(s)	*Studied effects*		*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
nausea_pp	AllocatedTreatment	METFORMIN vs PLACEBO	1.278	0.754	2.168	0.3626	0.4194

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47

*Analised using logistic regression (binary logit), probability modeled is Nausea_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.8.1 Vomiting - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Vomiting (n(%))	Yes	24 (20.3)	34 (31.2)	58 (25.6)
	No	94 (79.7)	75 (68.8)	169 (74.4)
Vomiting severity (n)	Mild	14	20	34
	Moderate	7	13	20
	Severe	3	1	4

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47
N = number of patients randomised, n = number of observations
Event with the highest severity picked for summary

By: Aryelly Rodriguez - ECTU Statistician

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Section 12. Maternal symptoms up to 36 weeks gestation

12.8.2 Vomiting - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Vomit_ana by AllocatedTreatment*

Vomit_ana(Vomit at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	34	24	58
No	75	94	169
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
vomit_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.775	0.970	3.249	0.0626	0.0687

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47

*Analised using logistic regression (binary logit), probability modeled is Vomit_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 12. Maternal symptoms up to 36 weeks gestation

12.9.1 Headache - from Visit 4 (18-20 Weeks) to Visit 6 (36 Weeks)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Any Headache (n(%))	Yes	40 (33.9)	37 (33.9)	77 (33.9)
	No	78 (66.1)	72 (66.1)	150 (66.1)
Headache severity (n)	Mild	21	24	45
	Moderate	13	9	22
	Severe	6	4	10

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N = number of patients randomised, n = number of observations
Event with the highest severity picked for summary

By: Aryelly Rodriguez - ECTU Statistician

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Section 12. Maternal symptoms up to 36 weeks gestation

12.9.2 Headache - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency — *Table of Headache_ana by AllocatedTreatment*

Headache_ana(Headache at least once from visit 4 to visit 7 (Y/N))	*AllocatedTreatment(Allocated Treatment)*		
	METFORMIN	*PLACEBO*	*Total*
Yes	37	40	77
No	72	78	150
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
headache_pp	AllocatedTreatment METFORMIN vs PLACEBO	1.002	0.578	1.737	0.9941	1.0000

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*Analised using logistic regression (binary logit), probability modeled is Headache_ana='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_12_1_Maternal symptoms_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 13. Serious Adverse Events

13.1.1.1 Mothers with at least one SAE

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Number of Patient with a SAE (n)	OVERALL	22	14	36

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Section 13. Serious Adverse Events

13.1.1.2 Mothers with at least one SAE - Statistical Analysis - POST-HOC*

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Frequency

Table of ANY_SAE by AllocatedTreatment

	AllocatedTreatment(Allocated Treatment)		
ANY_SAE	*METFORMIN*	*PLACEBO*	*Total*
No	95	96	191
Yes	14	22	36
Total	109	118	227

Parameter(s)	*Studied effects*	*Odds Ratio Estimate*	*Lower 95% Confidence Limit for Odds Ratio*	*Upper 95% Confidence Limit for Odds Ratio*	*P-value#*	*Fisher exact P-value#*
pat_sae_pp	AllocatedTreatment METFORMIN vs PLACEBO	0.643	0.311	1.331	0.2344	0.2767

EMPOWaR Statistical Analysis Report - Final 02 - tables run on: 05MAR2016 at 02:47

*Analised using logistic regression (binary logit), probability modeled is ANY_SAE='Yes'

#Significance level set at p<0.05

Detailed analysis in file 'Empowar_13_1_1_Npatients_SAE_analysis.lst'

By: Aryelly Rodriguez - ECTU Statistician

Section 13. Serious Adverse Events

13.1.1.3 SAE related to the mothers

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Number of SAE (n)	OVERALL	28	19	47
Number of SAE by relationship (n)	Possibly	2	2	4
	Unrelated	26	17	43
Number of SAE by expectedness (n)	Yes	6	6	12
	No	21	13	34
	Unk	1	0	1

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Section 13. Serious Adverse Events

13.1.1.3 SAE related to the mothers (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of SAE by outcome (n)	Missing	1	0	1
	Completely recovered	24	16	40
	Condition improving	1	1	2
	Condition improving | Completely recovered	1	0	1
	Condition improving | Recovered with sequelae	0	1	1
	Recovered with sequelae	1	1	2

Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
11136	METFORMIN	19JAN2012	14JAN2012	Diagnosis: Placental abruption. Drescription: Patient presented at 35+2 weeks gestation with a minor ante-partum haemorrage. Clinical diagnosis of placental abruption was made. necessitating immediate delivery by caesarean section. Diagnosis was confirmed at delivery. Mother and baby are both well. Severity: Moderate	Involved or prolonged inpatient hospitalisation| Life-threatening		Unrelated	No	Completely recovered	17JAN2012
11501	METFORMIN	14NOV2012	27OCT2012	Diagnosis: Unknown Description: Admitted with severe renal pain and vomiting. Noted to have deranged LFTs. Recent course of amoxicillin from GP for chest infection. Symptoms and LFTs resolved spontaneously. Severity: Mild	Involved or prolonged inpatient hospitalisation		Possibly	Yes	Completely recovered	31OCT2012
11748	METFORMIN	12DEC2013	11DEC2013	Diagnosis: Mastitis. Description: Sepsis secondary to Mastitis. Follow-up 20/02/14: Admitted 10 days postnatal with mastitis. Treated with IV then oral antibiotics. Severity: Moderate	Involved or prolonged inpatient hospitalisation	UTI. 25/09/2013 - 27/09/2013. medication required.	Unrelated	No	Completely recovered	14DEC2013
11748	METFORMIN	27SEP2013	25SEP2013	Diagnosis: Pain and Vomiting. Description: Self presented with upper abdominal pain and vomiting. ?UTI. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Depression from 2009 to 2010. Urinary Tract Infection. April 5th 2013 to 6.4.2013.	Unrelated	No	Recovered with sequelae	27SEP2013
11748	METFORMIN	07OCT2013	06OCT2013	Diagnosis: Abdominal Pain ? Preterm Labour Description: Self presented with abdo pain. ?Preterm labour complicated by urinary tract infections. Severity: Moderate Follow-up 20/02/14: Diagnosis: UTI. Admitted at 32 weeks gestation with abdominal pain. Urine culture +ve for e.coli. Threatened pre-term labour excluded. Treated with antibiotics and resolved. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Urinary Tract Infection. 02/04/13 - 05/04/2013 and 25/09/2013 - 26/09/2013. medication required for both infections.	Unrelated	No	Completely recovered	09OCT2014
11797	METFORMIN	18NOV2013	14NOV2013	Diagnosis: Vomiting in late pregnancy. Description: Self presented with excessive vomiting. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Hyperemesis. 20/05/13. ongoing. medication required.	Possibly	Yes	Completely recovered	15NOV2013
11881	METFORMIN	07JAN2014	30DEC2013	Diagnosis: Severe Sepsis. Description: Admitted at 30+4 weeks gestation with pyrexia. rigors and dysuria. Treated with multiple antibiotics for presumed urosepsis. Clinical deterioration over the course of a week. Decision made to deliver baby in maternal interest at 31+2 weeks gestation. Patient transferred to ITU for ventilatory support post delivery. Continues to improve. back in normal ward at present. Follow-up 14/01/14: Diagnosis: Probable urosepsis and atypical pneumonia necessitating preterm delivery in maternal interest. Description: Condition now resolved. patient recovered. Severity: Severe.	Life-threatening| Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	13JAN2014
12008	METFORMIN	13FEB2012	09FEB2012	Atonic uterus resulting in massive obstetric haemorrage. 2 litre loss. Severity: Severe	Life-threatening	N/a	Unrelated	No	Completely recovered	12FEB2012
12008	METFORMIN	16AUG2012	14FEB2012	Diagnosis: Chest Pain Description: Chest pain following LSCS 5/7 days after delivery. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	16FEB2012
13082	METFORMIN	07FEB2012	04FEB2012	Admitted for labile BP at 39 weeks. Commenced on labetalol 100mgs BD and IOL booked. Inpatient on Mat ward since 04/02/12. Completion of data 09/05/13: Participant delivered on 08.2.12 and was discharged on 11.2.12. On review of medical notes. hypertension resolved postnatally; was not discharged on any anti-hypertensives. Severity: Mild	Involved or prolonged inpatient hospitalisation	Has history of hypertension. was on Irbesartan 75mgs daily in 2009. Not on treatment since	Unrelated	Yes	Completely recovered	11FEB2012
13209	METFORMIN	31AUG2012	24AUG2012	Diagnosis: Inpatient stay for over 24hrs for investigations. All negative. Description: Reported chest pain and calf pain at day 4 postnatal. Admited to hospital for 2 days for chest x-ray and blood tests to rule out PE. Was commenced on Fragmin for 6/52 and attended for leg Doppler x 2. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	04SEP2012

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Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
13551	METFORMIN	05MAR2013	02MAR2013	Diagnosis: Emcs for fetal distress. followed by 5000ml PPH and hysterectomy. Description: Background: NI has been having close monitoring in pregnancy for raised BP. She was commenced on labetalol on 2.1.13. Had subsequent admission for raised BP 6.2.13 (not an SAE according to protocol). Discharged back to community care the following day. Admitted to antenatal ward again with raised BP on 25.2.13. Remained an inpatient until IOL commenced 28.2.13 at 20.30 at 38 weeks gestation. Baby: EMCS for fetal distress (CTG and FBS) under GA. Baby delivered at 1913. apgars 4 at 1 minute. 9 at 10 minutes. Cord PH's 7.18. 7.24. Baby was admitted to NICU overnight due to NI being transferred to Whiston. Re-united with mum when returned to Liverpool Women's. NI: Following emcs NI suffered from major haemorrhage totalling 5000ml. A hysterectomy was undertaken. NI received a total of 7 units of blood (including 500ml cell salvaged blood) and 1 unit of FFP. She also had a dextrose infusion to correct transfusion-related hypo	Involved or prolonged inpatient hospitalisation| Life-threatening	Raised BP. start 2.1.13. ongoing. medication required.	Unrelated	Yes	Condition improving | Recovered with sequelae	07MAR2013
14303	METFORMIN	08AUG2013	08AUG2013	Post Partum Haemorrhage 1200mls.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	08AUG2013
16121	METFORMIN	24JUN2013	30MAY2013	Diagnosis: Pyelonephritis Description: Pyelonephritis - ascending UTI involving pyelum. fever. tachycardia. abdo/back pain. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	04JUN2013
25232	METFORMIN	17OCT2013	14OCT2013	Diagnosis: Preterm Labour Spontaneous Rupture of Membranes. Description: Spontaneous rupture of membranes occurred 14/10/2013 at 13.30. No uterine activity. On 15/10/2013 developed maternal tachycardia and increase of white blood cells. Decision made at 10:50 on 15/10/13 to induce labour. Labour augmented with syntocinon infusion. Live baby girl born on 16/10/2013 at 07.14hrs. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	16OCT2013
25264	METFORMIN	15AUG2013	08AUG2013	Diagnosis: benign Intracranial Hypertension. Description: Admitted to Hallamshire Hospital with headache due to this. Had lumbar puncture to drain some CSF. Symptoms resolved. had one night in hospital. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Benign Intracranial Hypertension. started in 2009. ongoing. medication not required.	Unrelated	No	Completely recovered	09AUG2013
25264	METFORMIN	01OCT2013	26SEP2013	Diagnosis: Raised intra-cranial pressure. Description: Admission to Chesterfield Royal Hospital with headache. blurred vision. tinnitus. nausea 26/09/13. Lumbar puncture eased symptoms but backache marked after procedure and thought to be related to same. Care continued with analgesic therapy and physio. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Idiopathic Intracranial Hypertension. start spring 2009. end late 2011. and received medication between these dates. Diagnosed in 2009. ongoing and no medication required as contra-indicated in pregnancy.	Unrelated	Yes	Condition improving	.
25459	METFORMIN	11APR2014	06APR2014	Diagnosis: Left Calf Pain ?Thrombosis. Description: Admitted with unilateral calf pain. No redness or swelling. x1 dose anti-coagulant and analgesia given. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	07APR2014
25459	METFORMIN	17JUN2014	16JUN2014	Diagnosis: Right ovarian cyst Admitted to birth centre with right sided abdominal pain on 16.06.14. C/section performed 17.06.14. Severity: Mild	Involved or prolonged inpatient hospitalisation	Right adnexal cyst (15/03/14)	Unrelated	No	Completely recovered	17JUN2014
11323	PLACEBO	29MAY2012	20MAY2012	Diagnosis: Inconclusive Description: Admitted with shortness of breath and chest pain at 32 weeks gestation. Investigated thoroughly with CTPA. upperabdo ultrasound and blood tests but all investigation negative. Symptoms settled spontaneously. Severity: Moderate	Involved or prolonged inpatient hospitalisation	Asthma. ongoing. medication required Smoker. ongoing	Unrelated	No	Completely recovered	22MAY2012
11335	PLACEBO	21JUN2012	19JUN2012	Diagnosis: Post partum haemorrhage Description: Delivered by elective caesarian section on 19/06/12. Developed bleeding secondary to uterine atony following delivery while in recovery area. Rushed to theatre for EUA under GA. Haemorrhage managed with Bakri balloon. Estimated blood loss 2000mls. Severity: Moderate	Involved or prolonged inpatient hospitalisation| Life-threatening		Unrelated	No	Completely recovered	21JUN2012
11714	PLACEBO	30SEP2013	27SEP2013	Diagnosis: Large Blood Loss - 1500ml. Description: Emergency c/s for failure to progress in labour. 1500ml blood loss at delivery. Follow-up 20/02/14: Diagnosis: Post Partum Haemorrhage. Atonic postpartum haemorrhage following emergency caesarean section for failure to progress in the 1st stage of labour. Estimated blood loss 1500ml. Severity: Moderate.	Life-threatening| Involved or prolonged inpatient hospitalisation	Gestational Diabetes Mellitis. 09/07/13. ongoing. no medication required.	Unrelated	No	Completely recovered	03OCT2013

Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
11940	PLACEBO	04JUN2014	02JUN2014	Diagnosis: Respiratory Tract Infection. Presented with cough and feeling generally unwell at 37+ weeks gestation. Already taking amoxicillin and prednisolone prescribed by GP. Also complaining of reduced fetal movements. Admitted to hospital for optimisation of treatment and observation. Chest xray normal. Reviewed by respiratory physician and symptoms felt to be improving. likely viral origin. no further antibiotics or prednisolone required. advised to monitor PEFR and for GP to refer to outpatient respiratory clinic as necessary. Following Obstetric review. in view of persistently reduced fetal movements and recent diagnosis of gestational diabetes decision made for induction of labour. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	04JUN2014
13007	PLACEBO	05AUG2011	28JUL2011	Diagnosis: prolonged hospital stay. Participant induced for suspected IUGR at 40 weeks+1day. Baby's BW below 9th centile. therefore needed blood sugar recordings (TBGs) pre and post feeds as per protocol. Baby BW 2.72kgs. These were completed within 24hrs. This resulted in a prolongation of hospital stay. 12/08/2011 IUGR is an Expected outcome and is being routinely collected as a secondary outcome of this study. Therefore. not a SUSAR but a SAR.	Involved or prolonged inpatient hospitalisation	2008 - normal vaginal delivery at tern (41 weeks). 3100gms	Possibly	Yes	Completely recovered	28JUL2011
13144	PLACEBO	11MAY2012	31MAR2012	Diagnosis: Symphysis Pubis Pain. Physiological Faints in Pregnancy Description: Occasional fainting episodes and episodes of raised BP over past 6 weeks. 48hrs admission on ward for observation due to this. Also reports SPD. IOL at 36+7 booked for this reason. However on admission to IOL suite was found to be 36+6. reasons for IOL did not warrant delivery at this gestation. had been incorrectly calculated when IOL booked. therefore IOL rebooked and performed at 38+1 on 22/05/12. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	22MAY2012
13301	PLACEBO	19OCT2012	17OCT2012	Diagnosis: Intrapartum and postpartum haemorrhage of 2000mls Description: This lady was iduced at 41+5 for postdates pregnancy. She received 2mg x 2 of Prostin gel. Prior to ARM she had fresh bleeding PV. Oblique breech lie was diagnosed on USS. She was taken to theatre for emergency caesarean section. Intrapartum haemorrhage = 1000ml. postnatal haemorrhage = 1000ml. Total EBL = 2000ml. Baby born with Apgars 10 at 1 minute and 10 at 5 minutes. Cord ph's 7.26 and 7.28. Baby's weight = 4440g. AF well on demand. The lady was transfused 2 units of blood in theatre. Condition currently improving. today Hb 7.8g/dl. for further 2 units of blood. Follow-up 24/10/12: This lady was discharged home with baby from the postnatal ward on Sunday 20.10.12 at 14.00. Her HB was 8.7g/dl and she was prescribed ferrous sulphate 200mg TDS. Severity: Severe	Involved or prolonged inpatient hospitalisation| Life-threatening	Previous PPH and subsequent blood transfusion in 2007. medication required. PCOS. ongoing. no medication required.	Unrelated	Unk	Completely recovered	20OCT2012
13473	PLACEBO	04JAN2013	03JAN2013	Diagnosis: Neonatal BM's low. Baby admitted to NICU. lowest BM 1.7mmol Description: EP was delivered via emergency c/s. IOL at 36+3 for pre-eclampsia on 3.1.13. Baby was transferred to the neonatal unit for 24 hours post delivery for low BM's. Lowest BM 1.7mmol. baby tube fed only. no IV fluids required. Baby maintaining BM's and back on postnatal ward with mum after 24 hours. Discharged home 5.1.13. no follow-up anticipated. Severity: Mild	Involved or prolonged inpatient hospitalisation		Possibly	Yes	Completely recovered	04JAN2013
13591	PLACEBO	07MAY2013	30APR2013	Diagnosis: Hospital admission via ambulance with gall stones. Description: RB was admitted to Royal Liverpool Hospital on 30.04.13 via ambulance with chronic back pain. She is 3 weeks postnatal. Was kept nil by mouth for 24 hours and had a USS which diagnosed gall stones. Received antibiotics and analgesia whilst an inpatient and was discharged on 01.05.13. RB reports awaiting blood tests to see if presence of infection and has an appointment with a consultant at the Royal on 16.04.13. NB. Information obtained verbally from the patient only. no access to medical notes as attended a different hospital. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	01MAY2013
13705	PLACEBO	02AUG2013	19JUL2013	Diagnosis: APH 31+2/40. Description: Patient admitted to antenatal ward with APH at 31+2/40. Had x 2 small PV bleeds at home. HVS sent. Speculum NAD. Discharged home after 24 hours as nil further PV bleeding. Taking ferrous sulphate. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	20JUL2013
13712	PLACEBO	02AUG2013	23JUL2013	Diagnosis: Obstetric Choleostasis. Description: Patient presented at 31+5/40 with localised itching. Bile acids taken and indicate obstetric choleostasis. Patient prescribed Ursodeoxycholic acid 300mg TDS and Chlorphenamine 4mg. IOL booked for 05.09.2013. Having weekly bloods and CTG's. Information obtained from patient via telephone only. Severity: Moderate.	Other significant medical events (as defined in protocol)	Obstetric choleostasis in previous pregnancy in 2010. Start 27/01/2010. end 02/02/2010. medication required.	Unrelated	Yes	Completely recovered	06SEP2013
14336	PLACEBO	27NOV2013	26NOV2013	Diagnosis: Post partum haemorrhage and pre-eclampsia. Description: Admitted to High Dependency Unit from theatre recovery after total PPH 700mls (at delivery 400mls) requiring prolonged IV syntocinon treatment. In addition had raised BP requiring medication after admission to HDU. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Gestational Diabetes. started 07/11/2013. ongoing. no medication required.	Unrelated	No	Recovered with sequelae	29NOV2013

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Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
14336	PLACEBO	23OCT2013	17SEP2013	Diagnosis: Abdominal pain cause unknown. Description: Admitted with abdominal pain for observation. Cause unknown. Possible UTI. Possible 'uterine stretching pain'. Routine blood and urine tests performed. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	Yes	Completely recovered	23SEP2013
14336	PLACEBO	27NOV2013	20NOV2013	Diagnosis: Infective diarrhoea and vomiting. Description: Prolonged episode of diarrhoea and vomiting causing dehydration. IV fluid rehydration required on admission to hospital on 23/11/2013. Admitted for 24 hours. Had one stat dose labetalol for raised BP whilst an inpatient. Stopped study medication. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Gestational diabetes, started 07/11/2013. ongoing. no medication required.	Unrelated	No	Completely recovered	24NOV2013
14354	PLACEBO	20DEC2013	17DEC2013	Diagnosis: Threatened pre term labour. Description: G5 P2 33 weeks. admitted with PV bleed and irregular tightenings 17.12.13. Prescribed betamethasone and dalteparin. Hospitalised for observation. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Condition improving | Completely recovered	20JAN2014
15034	PLACEBO	07NOV2013	24OCT2013	PPH 1600mls. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	25OCT2013
17036	PLACEBO	12MAR2013	10MAR2013	Diagnosis: Influenza. Description: Inpatient hospitalisation due to influenza. Patient admitted on 10/03/13. Self discharged on 11/03/13 as feeling better. Study medication stopped whilst unwell. to recommence when well. Severity: Moderate. Follow-up 17/06/2014: Diagnosis: Influenza - resulting in raised ALTs requiring scan. Initial SAE reported due to hospitalisation due to influenza. Following this raised ALT levels were noted and a liver scan arranged. This showed an enlarged spleen ?consistent with recent influenza. This patient has had raised ALT levels dating back to 2010. Discharged home following scan.	Involved or prolonged inpatient hospitalisation| Other significant medical events (as defined in protocol)	Cholecystectomy. 2010 - 30/07/2010.	Unrelated	No	Completely recovered	17JUN2014
17137	PLACEBO	27DEC2013	25DEC2013	Diagnosis: Costochondritis. Description: Admitted with upper abdominal pain - bloods and USS all NAD. Presumed costochondritis. Discharged home 27/12/13. Severity:	Involved or prolonged inpatient hospitalisation	Previous episode of costochondritis	Unrelated	No	Completely recovered	27DEC2013
17137	PLACEBO	20JAN2014	17JAN2014	Admitted to antenatal ward with unstable lie. To remain inpatient until LSCS 24.1.14.	Involved or prolonged inpatient hospitalisation	Episode of costa chondritis	Unrelated	No	Completely recovered	21FEB2014
21033	PLACEBO	23MAY2014	27APR2014	Diagnosis: Abdominal Pain. Likely Costochondritis. Description: Admitted at 33+4 weeks gestation with abdominal pain. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	29APR2014
21033	PLACEBO	23MAY2014	11APR2014	Diagnosis: Likely Costochondritis. Description: Admitted at 31+2 weeks gestation for observation/monitoring for left sided chest pain. Investigations generally NAD. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Condition improving	.
21033	PLACEBO	02APR2014	28DEC2013	Diagnosis: Non-specific chest pain. Description: Admitted via ambulance with suspected clinical suspicion of a pulmonary embolism. Had left pleuritic chest pain. with shortness of breath and collapse. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Caesarean Section. 03/12/2013.	Unrelated	No	Completely recovered	30DEC2013
21069	PLACEBO	19MAR2014	18FEB2014	Diagnosis: Sepsis. Description: Pyrexial and tachycardic in labour. Raised CRP and white cell count. also platelets reduced. Had IV antibiotics. then oral. Went on septic pathway. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	25FEB2014
21093	PLACEBO	23DEC2013	28NOV2013	Diagnosis: Small antepartum haemorrhage. Description: Admitted to maternity ward overnight for observation as PV bleed. Ectropion noted on cervix. Placenta not low-lying. No pain. 23 weeks gestation. Severity: Mild	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	29NOV2013
21109	PLACEBO	09APR2014	03APR2014	Diagnosis: Small APH - nil on examination. Description: Admitted to maternity ward via maternity day unit with lower abdo discomfort/Braxton hicks/red pv loss/unstable lie. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Gestational Diabetes. 19/03/2014 - 08/04/2014.	Unrelated	No	Completely recovered	05APR2014
21109	PLACEBO	19MAR2014	14FEB2014	Diagnosis: Urinary Tract Infection. Description: Symptomatic of UTI and leukocytes in urine. Admitted for treatment and observation to maternity ward for over 12 hours. Severity: Mild.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	21FEB2014

Section 13. Serious Adverse Events

13.1.2 SAE related to the mothers - Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
25391	PLACEBO	12MAR2014	07MAR2014	Diagnosis: 1). Musculoskeletal Pain. 2). Depression. Description: Admitted to hospital for observation and analgesia for musculoskeletal pain and depression. Severity: Mild.	Involved or prolonged inpatient hospitalisation	Depression/ Anxiety. started 2005. ongoing. medication required.	Unrelated	No	Missing	.
53072	PLACEBO	30JUN2014	27JUN2014	Diagnosis: Episode of fitting. unknown cause. Description: Singular episode of fitting 5 days postnatal. unknown cause. Admitted to hospital via ambulance. MRI. CT. Chest X ray and blood tests carried out. No abnormality found. declined inpatient stay overnight for observation and had same day discharge. For follow up at 'first fit' clinic. Severity: moderate. UPDATE (01 Oct 2014): Diagnosis: Further reported 4-5 episodes of left sided numbness and tingling on upper body and face. Description: Reported 4 or 5 acute episodes of tingling commencing in left hand and ascending left side of body to face resulting in a heaviness and numb sensation. All occurred within 3 weeks of P/N fit episode and lasted around 5 minutes in duration. Nil since. Has had further ECG at neurology clinic which was normal. Still awaiting results of EEG and MRI.	Involved or prolonged inpatient hospitalisation| Other significant medical events (as defined in protocol)		Unrelated	No	Completely recovered	27JUN2014

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DOI: 10.3310/eme03070

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Section 13. Serious Adverse Events

13.2.1 SAE related to the babies

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo N=118*	*Metformin N=109*	*Overall N=227*
Number of Patient with a SAE (n)	OVERALL	12	5	17
Number of SAE (n)	OVERALL	12	5	17
Number of SAE by relationship (n)	Possibly	1	3	4
	Unrelated	11	2	13
Number of SAE by expectedness (n)	Yes	1	0	1
	No	11	5	16

Section 13. Serious Adverse Events

13.2.1 SAE related to the babies (Cont.)

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of SAE by outcome (n)	Completely recovered	8	2	10
	Condition still present and unchanged	2	2	4
	Death	1	0	1
	Recovered with sequelae	1	1	2

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DOI: 10.3310/eme03070

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Section 13. Serious Adverse Events

13.2.2 SAE related to the babies - Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
13670	METFORMIN	26JUL2013	21JUL2013	Diagnosis: Bilateral undescended testes. Description: Baby diagnosed with bilateral undescended testes. Baby born via normal vaginal delivery on 21/07/13. Undescended testes noted on 1st exam of the newborn. conducted by community midwife at home on 23/7/13. Baby otherwise well. referred to Alder Hey for follow-up. Severity: Moderate	Congenital anomaly/birth defect		Unrelated	No	Recovered with sequelae	26JUL2013
21095	METFORMIN	21MAR2014	20MAR2014	Diagnosis: No diagnosis yet. Description: Baby transferred to neonatal unit jittery/poor feeding/low BMS. Informed by paed. had significantly low BM's/hypoglycaemia. Raised lactate levels. Septic screen. Severity: Moderate.	Other significant medical events (as defined in protocol)| Involved or prolonged inpatient hospitalisation	Depression (Parent) prior to pregnancy. ongoing. medication required. Urine Infection (Parent). 17/03/2014. ongoing. medication required.	Possibly	No	Completely recovered	23MAR2014
21099	METFORMIN	21MAR2014	15MAR2014	Diagnosis: Significant Neonatal Jaundice. Description: Baby admitted from home to paediatric ward with significant neonatal jaundice. Phototherapy treatment required. Severity: Severe.	Involved or prolonged inpatient hospitalisation| Other significant medical events (as defined in protocol)	Raised BP (Parent). 06/03/2014 - 12/03/2014. no medication required.	Unrelated	No	Completely recovered	18MAR2014
25135	METFORMIN	09JUL2013	08JUL2013	Diagnosis: Congenital Malformation. Description: Circular thoracic lumbar spine lesion. Central 1 x 0.5cm vascular area. within 3 x 1cm area of hypopigmentation. (No hair). ? vascular malformation / occult spinal dysraphism. Follow-up 12/11/13: Diagnosis of Aplasia Cutis Congenita made 11/09/13. Severity: Mild Follow-up 28/01/14: Dermatologist reports evidence of Livedo. more likely livedo racemosa. Investigating for systemic connective tissue disease and full lupus screen. Mother reported (09/01/14) clonus in all 4 limbs of infant therefore referred to neurologist to investigate any central nervous system vasculopathy or abnormality. Severity: Moderate.	Congenital anomaly/birth defect		Possibly	No	Condition still present and unchanged	.
25459	METFORMIN	29JAN2014	28JAN2014	Diagnosis: Left unilateral talipes. Description: Had anomaly scan at 20 weeks gestation - the baby was noted to have left unilateral talipes. Severity: Moderate. Follow-up 01/07/14: Diagnosis: Fixed Talipes left foot. Fixed talipes. Back/hips normal. Initial ponseti plaster applied. To be replaced weekly and continue correction programme. Detected on 20/40 anomaly scan. Severity: Moderate.	Congenital anomaly/birth defect	Mother: Right adrenal cyst. started 15/11/2013. ongoing.	Possibly	No	Condition still present and unchanged	.
11536	PLACEBO	17JUN2013	09MAR2013	Diagnosis: Infection. SVT. Description: baby admitted to RHSC. Edinburgh at 8 days old. diagnosed with an infection at that time. At 12 days old diagnosed with SVT. Severity: Moderate	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	23MAR2013
11851	PLACEBO	08APR2014	03APR2014	Diagnosis: Right testicular hydrocele. abnormal left testicle. Description: Right testicular hydrocele. abnormal left testicle. Awaiting ultrasound scan and paediatric surgical review. Severity: Mild.	Congenital anomaly/birth defect		Unrelated	No	Condition still present and unchanged	.
12016	PLACEBO	10SEP2012	21APR2012	Diagnosis: Meconium Aspiration 1. Meconium Aspiration 2. Persistent Pulmonary Hypertension Severity: Severe	Involved or prolonged inpatient hospitalisation| Life-threatening		Unrelated	No	Completely recovered	28APR2012
13496	PLACEBO	14FEB2013	11FEB2013	Diagnosis: Baby admitted to NICU for low blood glucose Description: EH diagnosed as gestational diabetic at 36 weeks. managed on diet control only. Had elective caesarian section on 11.02.13 at 11am. Baby cord blood 2.4mmol. was grunting and had low TBG's on ward. Was admitted to NICU at 22.35 hours 11.02.13. Discharged back to ward with mum at 14.15 the next day 12.02.13. Mum and baby discharged home 13.02.13 baby asymptomatic of hypoglycaemia and BF well on discharge. No anticipated follow up. Severity: Mild	Involved or prolonged inpatient hospitalisation		Possibly	Yes	Completely recovered	13FEB2013
13591	PLACEBO	26JUL2013	20APR2013	Date of onset: ?? 20/04/2013 (i.e. from 2 weeks old - see below). Diagnosis: Baby developed vascular malformation. Description: Baby diagnosed with a venous malformation on upper shoulder. The baby was born on 6th April and nil was noted at birth or on the first paediatric examination. At the 6 week postnatal check with the GP a birth mark was noted and thought to be a haemangioma of infancy. I saw mum at 3 month postnatal visit on 4th July. when I first became aware of the birth mark. but as it wasn't picked up until the baby was 6 weeks old. this was outside of the 28 day postnatal reporting period for EMPOWaR. Mum has since been in touch to say that the birth mark has now been diagnosed as a venous malformation as it is the blood vessels below the actual mark which are causing it to grow and cause a lump. On further questioning mum thinks that the mark may have been there since 2 weeks of life but initially very small. Baby has been referred to a specialist at Alder Hey for management and possible removal	Congenital anomaly/birth defect	See previous SAE dated 7.5.13: Mother had hospital admission for gall stones at 24 days post natal. Having follow up at Royal Liverpool Hospital.	Unrelated	No	Recovered with sequelae	26JUL2013

Section 13. Serious Adverse Events

13.2.2 SAE related to the babies - Details

Population = Per-Protocol (PP) - AllocatedTreatment used for summarisation

Subject Number	Allocated Treatment	SAE - date of report	SAE - date of event	Description of SAE	Expedited Reporting Criteria	Relevant History	SAE_related_coded	SAE_expected_coded (Y/N)	SAE_outcome_coded	SAE - date of recovery
14413	PLACEBO	03MAR2014	03MAR2014	Diagnosis: Baby delivered with some abnormalities. Description: C/section at 3/3/14 at 12.30 - baby found to have abnormal toes. fingers and anteriorly placed anus. Left hand is normal. Right hand has a middle short finger with hypoplastic nail and is twisted. Index finder has an accessory digit. On the right foot the big toe has syndactyly and the 3rd toe is not formed. On the left foot. the big toe is syndactyly and the 3rd toe not formed. There is only one centimetre between the anus and the posterior forchette. Severity: Severe.	Congenital anomaly/birth defect		Unrelated	No	Condition still present and unchanged	.
21018	PLACEBO	05NOV2013	17OCT2013	Diagnosis: Presumed Sepsis/Pneumonia consolidation. Description: Admitted to neonatal unit shortly after birth for investigations for spreading vascular lesions on truck. grunting and tachypnoeic. Remained on neonatal unit 17 - 22/10/13. Severity: Moderate	Involved or prolonged inpatient hospitalisation	Vascular lesions. grunting. tachypnoeic. pneumonia. started 17/10/2013. ended 22/10/2013. medication required.	Unrelated	No	Completely recovered	24OCT2013
21038	PLACEBO	16JAN2014	31DEC2013	Diagnosis: Cyanotic episodes. likely vasomotor phenomenon. Description: Admitted to ward 8 via ambulance/A&E 7 days old with cyanotic episodes 10 times a day lasting 3 - 5 mins. Investigations all normal. Discharged home 02/01/2014. No further admissions. Severity: Moderate.	Involved or prolonged inpatient hospitalisation		Unrelated	No	Completely recovered	02JAN2014
21047	PLACEBO	22APR2014	22JAN2014	Diagnosis: RSV positive bronchiolitis. Description: Admitted to paediatric ward at 2 weeks old with cough and increased work of breathing. Required oxygen and help with NG feeds for a few days. Gradually recovered. Severity: Moderate.	Involved or prolonged inpatient hospitalisation	Gestational Diabetes (Mother). 17/12/2013 - 08/01/2014.	Unrelated	No	Completely recovered	30JAN2014
21069	PLACEBO	19MAR2014	18FEB2014	Diagnosis: Meningitis/Sepsis. Description: Admitted to Neonatal Unit shortly after birth jittery/maternal sepsis. Had dusky episodes/desaturations/apnoeas/jaundice/sepsis. Ventilated. Meningitis diagnosed. / Cerebral Haemorrhage. Severity: Severe.	Involved persistent or significant disability or incapacity| Involved or prolonged inpatient hospitalisation	Sepsis in labour/maternal infection (Parent). 18/02/2014 - 25/02/2014. medication required.	Unrelated	No	Completely recovered	07MAR2014
21119	PLACEBO	06JAN2014	02JAN2014	Diagnosis: Congenital Anomaly. Description: Anomaly ultrasound scan showed structural abnormalities to hands and feet. Appearances suggestive of split hand and foot syndrome. Severity: Severe	Patient died| Congenital anomaly/birth defect		Unrelated	No	Death	.
25320	PLACEBO	03FEB2014	31JAN2014	Diagnosis: ? Hirschsprungs in neonate. Description: Distended stomach on antenatal scans. At birth neonate admitted to NNU then transfer to tertiary centre same day (Nottingham Queen's Medical). Severity: Severe. Follow-up 27/02/2014: Subsequently resolved. no pathology. baby discharged. Severity: Severe.	Congenital anomaly/birth defect		Unrelated	No	Completely recovered	27FEB2014

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DOI: 10.3310/eme03070

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EMPOWaR: Efficacy of Metformin in Pregnant Obese Women, a Randomised Controlled Trial

Funding reference number: 08/246/09 (NIHR Efficacy and Mechanism Evaluation Programme)
EudraCT number 2009-017134-47

Statistical Report - Mechanistic paper (MP) - Final

Population = Intention to treat (ITT) - AllocatedTreatment used for analysis

Report number: 02

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Data set analysed as it was on:
29 April 2015

EMPOWaR Statistical Report MP (AllocatedTreatment used) - tables run on: 05MAR2016

By: Aryelly Rodriguez - ECTU Statistician

Section 1. Maternal body fat

1.1.1 Maternal Body mass (Edinburgh)*# - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BodyMass (kg) Visit 2	Mean	101.388	103.322	102.413
	Median	97.810	104.018	100.077
	SD	16.190	15.961	16.017
	MIN,MAX	74.97,170.25	73.54,140.37	73.54,170.25
	Q1,Q3	89.72,111.83	92.19,112.90	90.53,112.40
	n	47	53	100
	Nmiss	13	7	20
BodyMass (kg) Visit 6	Mean	108.794	113.366	111.043
	Median	105.046	111.525	108.272
	SD	14.871	16.740	15.853
	MIN,MAX	79.82,165.47	78.11,147.87	78.11,165.47
	Q1,Q3	100.32,117.60	104.43,124.68	102.65,118.64
	n	31	30	61
	Nmiss	29	30	59

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By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 1. Maternal body fat

1.1.1 Maternal Body mass (Edinburgh) (Cont.)*# - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BodyMass (kg) Visit 9	Mean	102.821	106.471	104.677
	Median	102.540	105.399	104.190
	SD	12.759	16.507	14.772
	MIN,MAX	72.74,126.73	73.76,146.86	72.74,146.86
	Q1,Q3	96.36,112.37	98.50,115.30	96.80,114.25
	n	29	30	59
	Nmiss	31	30	61

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 1. Maternal body fat

1.1.2.1 Maternal Body fat mass (Edinburgh)*# - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 2	Mean	47.93	50.32	49.19
	Median	45.85	49.38	47.51
	SD	12.05	11.79	11.92
	MIN,MAX	29.9,96.8	26.8,76.2	26.8,96.8
	Q1,Q3	38.6,54.4	42.2,59.5	41.2,55.5
	n	48	53	101
	Nmiss	12	7	19
FatMass (kg) Visit 6	Mean	50.83	54.37	52.57
	Median	50.28	54.58	50.69
	SD	10.94	12.17	11.61
	MIN,MAX	27.4,89.2	30.5,76.4	27.4,89.2
	Q1,Q3	46.9,55.4	46.8,65.1	46.9,57.9
	n	31	30	61
	Nmiss	29	30	59

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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Section 1. Maternal body fat

1.1.2.1 Maternal Body fat mass (Edinburgh) (Cont.)*# - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 9	Mean	49.06	50.09	49.58
	Median	51.27	48.55	50.26
	SD	9.01	13.73	11.56
	MIN,MAX	26.6,63.2	13.6,75.8	13.6,75.8
	Q1,Q3	46.3,55.4	45.1,59.1	45.1,56.3
	n	29	30	59
	Nmiss	31	30	61

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 1. Maternal body fat

1.1.2.2 Fat mass (kg) - Statistical Analysis - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
MOTHER_FATMASS_V2_ALL_OBS - itt	51.623	1.2656	48	52.835	1.1788	53	1.212	-2.111	4.535	0.524	0.4708
MOTHER_FATMASS_V6_ALL_OBS - itt	53.538	1.6104	31	55.390	1.5907	30	1.852	-2.623	6.327	0.686	0.4108
MOTHER_FATMASS_V9_ALL_OBS - itt	50.860	1.8982	29	50.858	1.8299	30	-0.002	-5.227	5.223	0.000	0.9994

EMPOWaR Statistical Analysis Report MECHANISTIC PAPER - Final 02 - tables run on: 05MAR2016 at 03:54 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in table 1.1.2.1 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and c-section delivery. Significance level set at p<0.05
Estimated mean represents the adjusted means of the non-transformed variable by allocated treatment for V9,
SE represents standard error of the non-transformed estimated means and N represents number of observations for V9
*Represents the difference between non-transformed estimated means and CI Represents the 95% confidence interval for V9
Calculations and detailed analysis are presented in study file 'Empowar_1_1_2_BODPOD_fat_percent_ANALYSIS.lst'
All parameters shown normal or near-normal behavior

DOI: 10.3310/eme03070

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Section 1. Maternal body fat

1.1.2.3 Maternal Body fat mass(Edinburgh)*# - V2 and V6 data must be present (paired observations)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 2	Mean	48.75	52.70	50.72
	Median	47.57	53.50	50.10
	SD	13.23	11.72	12.55
	MIN,MAX	31.1,96.8	28.3,76.2	28.3,96.8
	Q1,Q3	40.5,54.9	42.5,61.8	42.4,58.7
	n	28	28	56
	Nmiss	0	0	0
FatMass (kg) Visit 6	Mean	50.92	53.91	52.41
	Median	49.99	52.80	50.51
	SD	11.49	12.37	11.93
	MIN,MAX	27.4,89.2	30.5,76.4	27.4,89.2
	Q1,Q3	47.2,56.2	45.8,62.9	46.8,58.4
	n	28	28	56
	Nmiss	0	0	0

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By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 1. Maternal body fat

1.1.2.3 Maternal Body fat mass (Edinburgh)(Cont.)*# - V2 and V6 data must be present (paired observations)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Change FatMass (%) V6 from V2$	Mean	5.66	2.47	4.06
	Median	3.79	0.74	1.21
	SD	10.34	7.31	9.02
	MIN,MAX	-11.8,32.9	-8.9,17.1	-11.8,32.9
	Q1,Q3	-1.5,12.1	-2.9,8.2	-1.9,10.2
	n	28	28	56
	Nmiss	0	0	0

EMPOWaR Statistical Analysis Report MECHANISTIC PAPER - Final 02 - tables run on: 05MAR2016 at 03:54

By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

$Change calculated as: ((FatMass_V6-FatMass_V2)/FatMass_V2)*100

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DOI: 10.3310/eme03070

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Section 1. Maternal body fat

1.1.2.4 Maternal Body fat mass (Edinburgh)*# - V2 and V9 data must be present (paired observations)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
FatMass (kg) Visit 2	Mean	48.98	54.52	51.85
	Median	50.10	54.85	51.95
	SD	9.68	11.16	10.74
	MIN,MAX	31.1,72.8	34.9,76.2	31.1,76.2
	Q1,Q3	42.7,54.4	44.9,63.1	42.9,58.2
	n	26	28	54
	Nmiss	0	0	0
FatMass (kg) Visit 9	Mean	48.48	50.81	49.69
	Median	50.58	49.49	50.13
	SD	9.30	13.75	11.77
	MIN,MAX	26.6,63.2	13.6,75.8	13.6,75.8
	Q1,Q3	43.3,55.4	45.3,59.9	45.1,56.3
	n	26	28	54
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 1. Maternal body fat

1.1.2.4 Maternal Body fat mass (Edinburgh)(Cont.)*# - V2 and V9 data must be present (paired observations)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Change FatMass (%) V9 from V2$	Mean	-0.38	-6.16	-3.38
	Median	-2.50	-2.63	-2.63
	SD	12.42	17.13	15.19
	MIN,MAX	-16.5,35.3	-80.1,12.0	-80.1,35.3
	Q1,Q3	-10.7,7.9	-11.9,3.1	-11.8,3.3
	n	26	28	54
	Nmiss	0	0	0

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By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

$Change calculated as: ((FatMass_V9-FatMass_V2)/FatMass_V2)*100

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Section 1. Maternal body fat

1.1.2.5 Fat mass (kg) (paired observations) and Change FatMass (%) V6 from V2 and V9 from V2$ - Statistical Analysis

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
MOTHER_FATMASS_V2_PAIRED_OBS - itt	52.105	1.6120	28	53.373	1.5617	28	1.268	-3.204	5.740	0.323	0.5720
MOTHER_FATMASS_V6_PAIRED_OBS - itt	53.907	1.6579	28	54.508	1.6062	28	0.601	-3.998	5.200	0.069	0.7942
MOTHER_FATMASS_V9_PAIRED_OBS - itt	50.320	2.0138	26	51.241	1.8984	28	0.921	-4.604	6.446	0.112	0.7392
MOTHER_FATMASS_PRCENT_CHNG_V2_V6 - itt	4.747	1.6482	28	2.285	1.5968	28	-2.461	-7.034	2.111	1.166	0.2852
MOTHER_FATMASS_PRCENT_CHNG_V2_V9 - itt	-1.298	2.9065	26	-6.376	2.7399	28	-5.078	-13.052	2.896	1.635	0.2069

EMPOWaR Statistical Analysis Report MECHANISTIC PAPER - Final 02 - tables run on: 05MAR2016 at 03:54 By: Aryelly Rodriguez - ECTU Statistician
Summary statistics are presented in tables 1.1.2.3 to 1.1.2.4 of this report
Outcome analysed using a linear regression model, ajusted by BMI band. Significance level set at p<0.05
Estimated mean represents the adjusted means of the non-transformed variable by allocated treatment
SE represents standard error of the non-transformed estimated means and N represents number of observations
*Represents the difference between non-transformed estimated means and CI Represents the 95% confidence interval for V9
Calculations and detailed analysis are presented in study file 'Empowar_1_1_2_BODPOD_fat_percent_ANALYSIS.lst'
All parameters shown normal or near-normal behavior
$Change calculated as: ((FatMass_V6-FatMass_V2)/FatMass_V2)*100 and ((FatMass_V9-FatMass_V2)/FatMass_V2)*100

Section 1. Maternal body fat

1.1.3 Maternal body percentage fat (Edinburgh)*# - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 2	Mean	46.82	48.19	47.54
	Median	46.85	48.00	47.50
	SD	5.62	5.18	5.41
	MIN,MAX	33.9,59.0	34.3,58.7	33.9,59.0
	Q1,Q3	42.6,50.4	45.3,51.7	44.8,51.1
	n	48	53	101
	Nmiss	12	7	19
Fat (%) Visit 6	Mean	46.30	47.48	46.88
	Median	47.10	47.65	47.30
	SD	4.84	4.63	4.74
	MIN,MAX	34.3,53.9	39.1,56.3	34.3,56.3
	Q1,Q3	43.9,48.8	43.9,51.2	43.9,50.2
	n	31	30	61
	Nmiss	29	30	59

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 1. Maternal body fat

1.1.3 Maternal body percentage fat (Edinburgh) (Cont.)*# - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 9	Mean	47.45	48.35	47.91
	Median	48.10	47.30	48.00
	SD	4.97	5.31	5.12
	MIN,MAX	36.6,54.6	37.9,58.6	36.6,58.6
	Q1,Q3	43.6,51.9	44.6,53.1	44.4,52.0
	n	29	30	59
	Nmiss	31	30	61

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 1.2 Neonatal body fat - Only Alive Births

1.2.1 Baby Body mass at Visit 8 (delivery) and Visit 9 (Final 3 months postnatal)# - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BABY_BodyMass* (kg)-V8	Mean	3.396	3.378	3.387
	Median	3.387	3.426	3.418
	SD	0.501	0.411	0.454
	MIN,MAX	2.42,4.45	2.50,3.99	2.42,4.45
	Q1,Q3	3.09,3.69	3.10,3.74	3.09,3.71
	n	22	21	43
	Nmiss	36	37	73
BABY_BodyMass* (kg)-V9	Mean	9.683	6.011	7.910
	Median	6.228	6.103	6.161
	SD	19.409	0.920	13.981
	MIN,MAX	4.80,112.37	4.41,8.01	4.41,112.37
	Q1,Q3	5.61,6.54	5.27,6.51	5.49,6.54
	n	30	28	58
	Nmiss	28	30	58

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat Mass and Body Mass was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 1.2 Neonatal body fat - Only Alive Births

1.2.2.1 Baby Fat Mass at Visit 8 (delivery) and Visit 9 (Final 3 months postnatal)#* - ALL AVAILABLE OBSERVATIONS

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BABY_FatMass* (kg)-V8	Mean	0.43	0.45	0.44
	Median	0.40	0.44	0.43
	SD	0.25	0.20	0.22
	MIN,MAX	0.0,1.0	0.1,0.8	0.0,1.0
	Q1,Q3	0.3,0.6	0.3,0.6	0.3,0.6
	n	22	21	43
	Nmiss	36	37	73
BABY_FatMass* (kg)-V9	Mean	3.01	1.42	2.24
	Median	1.54	1.43	1.49
	SD	8.05	0.50	5.80
	MIN,MAX	0.9,46.3	0.6,2.5	0.6,46.3
	Q1,Q3	1.2,1.9	1.0,1.7	1.2,1.8
	n	31	29	60
	Nmiss	27	29	56

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat Mass was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 1.2 Neonatal body fat - Only Alive Births - V8 and V9 data must be present (paired observations)

1.2.2.2 Baby Fat Mass at Visit 8 (delivery) and Visit 9 (Final 3 months postnatal)#*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BABY_FatMass* (kg)-V8	Mean	0.40	0.45	0.42
	Median	0.40	0.44	0.42
	SD	0.21	0.20	0.20
	MIN,MAX	0.0,0.8	0.1,0.8	0.0,0.8
	Q1,Q3	0.3,0.6	0.3,0.6	0.3,0.6
	n	16	15	31
	Nmiss	0	0	0
BABY_FatMass* (kg)-V9	Mean	4.35	1.47	2.95
	Median	1.53	1.46	1.52
	SD	11.20	0.50	8.06
	MIN,MAX	1.0,46.3	0.6,2.3	0.6,46.3
	Q1,Q3	1.3,1.8	1.0,1.8	1.2,1.8
	n	16	15	31
	Nmiss	0	0	0

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By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat Mass was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 1.2 Neonatal body fat - Only Alive Births - V8 and V9 data must be present (paired observations)

1.2.2.3 Baby Fat Mass percentange change$ from Visit 8 (delivery) to Visit 9 (Final 3 months postnatal)#*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BABY_FatMass change$ V8 to V9 (%)	Mean	1466.00	325.17	913.99
	Median	337.48	230.16	269.91
	SD	3183.06	311.85	2333.92
	MIN,MAX	63.0,12546	13.8,1139.8	13.8,12546
	Q1,Q3	165.4,571.0	106.2,433.7	158.7,515.8
	n	16	15	31
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Baby Fat Mass was only measured at the Edinburgh site
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks
$Percentange change calculated as ((B_FatMass_V9-B_FatMass_V8)/B_FatMass_V8)*100

Section 1.2 Neonatal body fat - Only Alive Births

1.2.2.4 Baby Fat Mass - Statistical Analysis

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
BABY_FATMASS_V8_PAIRED_OBS -	0.422	0.0545	16	0.445	0.0503	15	0.023	-0.130	0.177	0.098	0.7566
BABY_FATMASS_V9_PAIRED_OBS -	1.665	0.1279	15	1.456	0.1094	15	-0.208	-0.559	0.142	1.491	0.2326
BABY_FATMASS_CHANGE_V8_TO_V9#	1.232	0.1408	15	1.012	0.1205	15	-0.220	-0.606	0.165	1.376	0.2511
BABY_FATMASS_V8_ALL_OBS - itt	0.456	0.0517	22	0.447	0.0472	21	-0.010	-0.152	0.133	0.019	0.8905
BABY_FATMASS_V9_ALL_OBS - itt	1.599	0.0848	30	1.435	0.0833	29	-0.164	-0.398	0.070	1.970	0.1660

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Summary statistics are presented in tables 1.2.2.1 to 1.2.2.3 of this report
Outcome analysed using a linear regression model, ajusted by BMI band. Significance level set at p<0.05. Estimated mean represents the mean of the non-transformed variable by allocated treatment,Parameter shown normal or near-normal behavior
SE represents standard error of the estimated non-transformed mean and N represents number of observations
*Represents the difference between the estimated log means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file '1_2_2_PEAPOD_fat_percent_ANALYSIS.lst'
NOTE:Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks, outliers outside +/- 6SD were removed to exclude extreme errors in data entry
#Percentange change calculated as ((B_FatMass_V9-B_FatMass_V8)/B_FatMass_V8)*100

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Section 1.2 Neonatal body fat - Only Alive Births - ALL AVAILABLE OBSERVATIONS

1.2.3 Baby Fat % at Visit 8 (delivery) and Visit 9 (Final 3 months postnatal)#*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BABY_Fat* (%)-V8	Mean	12.08	12.86	12.46
	Median	10.95	12.30	12.30
	SD	5.74	4.47	5.11
	MIN,MAX	1.0,24.3	5.7,20.6	1.0,24.3
	Q1,Q3	8.1,17.1	10.0,16.2	8.1,16.5
	n	22	21	43
	Nmiss	36	37	73
BABY_Fat* (%)-V9	Mean	25.88	23.19	24.58
	Median	24.10	23.50	23.55
	SD	6.13	5.91	6.13
	MIN,MAX	15.1,41.6	12.0,32.3	12.0,41.6
	Q1,Q3	21.5,29.7	19.6,27.8	21.2,28.8
	n	31	29	60
	Nmiss	27	29	56

EMPOWaR Statistical Analysis Report MECHANISTIC PAPER - Final 02 - tables run on: 05MAR2016 at 03:54

By: Aryelly Rodriguez - ECTU Statistician

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Baby Fat % was only measured at the Edinburgh site

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 2. Hyperinsulinaemic euglycaemic clamp study

2.1 Maternal Age at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of patients in substudy-CLAMP (n)	Yes	11	9	20
Maternal Age at consent (years)	Mean	29.6	32.6	31.0
	Median	29.0	32.0	31.0
	SD	3.6	3.7	3.8
	MIN,MAX	25,37	25,38	25,38
	Q1,Q3	27,31	31,35	28,34
	n	11	9	20
	Nmiss	0	0	0

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.2 Previous pregnacy status* PARITY 1 at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
PARITY1 (n(%))	0	5 (45.5)	3 (33.3)	8 (40.0)
	=>1	6 (54.5)	6 (66.7)	12 (60.0)

N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 24 weeks or more were considered

Section 2. Hyperinsulinaemic euglycaemic clamp study

2.3.1 Maternal Calculated BMI at Baseline - Visit 2 (10-16 Weeks)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 2	Mean	35.7	37.9	36.7
	Median	36.1	38.2	36.4
	SD	3.5	4.4	4.0
	MIN,MAX	30,42	31,47	30,47
	Q1,Q3	32,39	36,39	34,39
	n	11	9	20
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.3.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 6	Mean	38.7	39.4	39.0
	Median	40.1	39.3	39.4
	SD	3.5	2.6	3.1
	MIN,MAX	33,43	36,43	33,43
	Q1,Q3	35,42	38,41	37,42
	n	11	8	19
	Nmiss	0	1	1
Calculated BMI (kg/m^2) change V6 baseli	Mean	3.0	2.6	2.8
	Median	2.4	2.3	2.4
	SD	2.1	1.8	1.9
	MIN,MAX	-0,7	0,6	-0,7
	Q1,Q3	1,5	1,4	1,4
	n	11	8	19
	Nmiss	0	1	1

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.3.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 9	Mean	35.7	37.9	36.6
	Median	36.7	37.4	37.2
	SD	4.0	4.1	4.1
	MIN,MAX	29,40	33,46	29,46
	Q1,Q3	31,39	35,40	35,39
	n	10	8	18
	Nmiss	1	1	2
Calculated BMI (kg/m^2) change V9 baseli	Mean	-0.1	-0.6	-0.3
	Median	-0.5	-0.7	-0.5
	SD	1.5	2.1	1.8
	MIN,MAX	-3,2	-5,2	-5,2
	Q1,Q3	-1,1	-1,1	-1,1
	n	10	8	18
	Nmiss	1	1	2

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.3.4 Maternal body percentage fat (Edinburgh)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 1	Mean	46.14	49.31	47.45
	Median	47.10	49.70	48.20
	SD	4.46	5.78	5.13
	MIN,MAX	39.6,52.4	41.6,57.1	39.6,57.1
	Q1,Q3	41.4,48.8	44.0,55.2	44.0,51.1
	n	10	7	17
	Nmiss	1	2	3
Fat (%) Visit 6	Mean	46.20	48.19	47.10
	Median	47.30	49.30	47.45
	SD	5.28	4.53	4.94
	MIN,MAX	34.3,53.5	41.1,55.8	34.3,55.8
	Q1,Q3	43.9,48.8	44.7,51.0	44.6,50.6
	n	11	9	20
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*This summary is only applicable to Edinburgh patients

#Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 2. Hyperinsulinaemic euglycaemic clamp study

2.3.4 Maternal body percentage fat (Edinburgh) (Cont.)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Fat (%) Visit 9	Mean	46.89	49.50	47.96
	Median	48.10	48.90	48.10
	SD	5.51	5.07	5.34
	MIN,MAX	36.6,52.4	42.2,56.7	36.6,56.7
	Q1,Q3	45.4,51.9	46.0,53.2	46.0,52.0
	n	10	7	17
	Nmiss	1	2	3

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.4.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 1 (days)	Mean	85.5	93.8	89.3
	Median	84.0	94.0	90.5
	SD	10.8	8.1	10.4
	MIN,MAX	72,102	82,106	72,106
	Q1,Q3	76,96	89,99	83,99
	n	11	9	20
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	96.5	101.0	98.5
	Median	94.0	101.0	99.0
	SD	9.2	7.3	8.5
	MIN,MAX	84,111	89,111	84,111
	Q1,Q3	89,102	97,107	93,105
	n	11	9	20
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value

Section 2. Hyperinsulinaemic euglycaemic clamp study

2.4.2 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 3 (days)	Mean	98.7	101.9	100.2
	Median	100.0	102.0	100.5
	SD	8.4	7.1	7.8
	MIN,MAX	87,113	89,111	87,113
	Q1,Q3	90,102	98,107	95,107
	n	11	9	20
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	150.5	141.7	146.6
	Median	149.0	141.0	145.5
	SD	7.3	4.5	7.5
	MIN,MAX	142,164	137,151	137,164
	Q1,Q3	145,154	139,141	141,151
	n	11	9	20
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.4.3 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 5 (days)	Mean	196.9	198.6	197.7
	Median	198.0	198.0	198.0
	SD	5.2	4.3	4.7
	MIN,MAX	190,207	193,205	190,207
	Q1,Q3	192,200	195,201	194,201
	n	11	9	20
	Nmiss	0	0	0
Calculated* Gestation - Visit 6 (days)	Mean	255.3	255.0	255.2
	Median	256.0	254.0	255.5
	SD	4.6	3.7	4.1
	MIN,MAX	245,263	251,263	245,263
	Q1,Q3	253,258	253,256	253,257
	n	11	9	20
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 2. Hyperinsulinaemic euglycaemic clamp study

2.4.4 Gestation by timepoint - Visit 7 Term, Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 7 (days)	Mean	282.0	282.0	282.0
	Median	282.0	283.0	282.0
	SD	4.5	3.6	4.0
	MIN,MAX	275,289	278,285	275,289
	Q1,Q3	281,283	278,285	281,283
	n	6	3	9
	Nmiss	5	6	11
Calculated* Gestation - Visit 8 (days)	Mean	282.1	280.9	281.6
	Median	283.0	278.0	283.0
	SD	9.9	8.3	9.0
	MIN,MAX	260,292	267,293	260,293
	Q1,Q3	281,289	277,285	278,288
	n	11	9	20
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.4.5 Gestation by timepoint - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Recorded* Gestation - Visit 8 (days)	Mean	280.5	280.6	280.6
	Median	282.0	278.0	282.0
	SD	8.5	8.2	8.1
	MIN,MAX	260,290	267,292	260,292
	Q1,Q3	277,287	276,285	277,287
	n	11	9	20
	Nmiss	0	0	0
Coded R_gestation - Visit 8 (n(%))	>37 WEEKS	11 (100)	9 (100)	20 (100)

Section 2. Hyperinsulinaemic euglycaemic clamp study

2.5.1 HOMA-IR - Visit 2 Consent/Baseline (10-16 Weeks) and Visit 5 (28 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
HOMA - visit 2	Mean	3.797	4.052	3.912
	Median	3.542	3.907	3.723
	SD	1.167	1.550	1.321
	MIN,MAX	2.37,6.51	2.21,6.55	2.21,6.55
	Q1,Q3	2.94,4.49	2.68,5.06	2.87,4.53
	n	11	9	20
	Nmiss	0	0	0
HOMA - visit 5	Mean	3.797	4.052	3.912
	Median	3.542	3.907	3.723
	SD	1.167	1.550	1.321
	MIN,MAX	2.37,6.51	2.21,6.55	2.21,6.55
	Q1,Q3	2.94,4.49	2.68,5.06	2.87,4.53
	n	11	9	20
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose x insulin / 22.5)

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2.5.2 HOMA-IR - Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
HOMA - visit 6	Mean	3.797	4.052	3.912
	Median	3.542	3.907	3.723
	SD	1.167	1.550	1.321
	MIN,MAX	2.37,6.51	2.21,6.55	2.21,6.55
	Q1,Q3	2.94,4.49	2.68,5.06	2.87,4.53
	n	11	9	20
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

HOMA-IR was calculated using the following formula: HOMA-IR (units) = (glucose x insulin / 22.5)

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.6.1 Calculated Z score (*)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of patients in substudy-CLAMP (n)	Yes	11	9	20
Z-score for birth weight centile_CLAMP	Mean	0.0123	1.2038	0.5140
	Median	0.1565	1.2843	0.3786
	SD	0.9957	1.0711	1.1672
	MIN,MAX	-1.834,1.815	-0.742,2.711	-1.834,2.711
	Q1,Q3	-0.370,0.501	0.662,1.885	0.044,1.624
	n	11	8	19
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

(*) Patient 11551 has been excluded from the summary

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Section 2. Hyperinsulinaemic euglycaemic clamp study

2.6.2 Calculated Z score - Statistical Analysis

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
z-score_CLAMP - itt	0.012	0.2930	11	1.204	0.3436	8	1.192	0.239	2.144	6.962	0.0172

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Summary statistics are presented in table 2.6.1 of this report. Patient 11551 has been excluded from the analysis
Outcome analysed using a linear regression model. Significance level set at p<0.05
Estimated mean represents the means for the z score by allocated treatment,
SE represents standard error of the estimated mean and N represents number of observations
*Represents the difference between the estimated means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_2_6_primary_outcome_z_analysis_CLAMP.lst'
Parameter shown normal behavior

Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.1.1 Maternal Age at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of patients in substudy-Endothe (n)	Yes	15	16	31
Maternal Age at consent (years)	Mean	31.5	27.3	29.3
	Median	32.0	26.0	31.0
	SD	4.4	6.1	5.7
	MIN,MAX	22,38	19,38	19,38
	Q1,Q3	29,34	22,32	25,34
	n	15	16	31
	Nmiss	0	0	0

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Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.1.2 Maternal smoking Status at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Smoking Status (n(%))	ACTIVE	1 (6.7)	3 (18.8)	4 (12.9)
	NOT SMOKING	14 (93.3)	13 (81.3)	27 (87.1)

Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.1.3 Maternal Blood Pressure at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Maternal Systolic BP (mmHg)	Mean	121.7	117.3	119.4
	Median	120.0	120.0	120.0
	SD	10.8	9.7	10.3
	MIN,MAX	108,140	100,134	100,140
	Q1,Q3	110,130	110,125	110,126
	n	15	16	31
	Nmiss	0	0	0
Maternal Diastolic BP (mmHg)	Mean	69.1	69.1	69.1
	Median	68.0	70.0	70.0
	SD	7.3	9.5	8.3
	MIN,MAX	60,80	54,84	54,84
	Q1,Q3	64,76	60,78	60,78
	n	15	16	31
	Nmiss	0	0	0

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Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.2 Previous pregnacy status* PARITY 1 at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
PARITY1 (n(%))	0	7 (46.7)	11 (68.8)	18 (58.1)
	=>1	8 (53.3)	5 (31.3)	13 (41.9)

N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 24 weeks or more were considered

Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.3.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 2	Mean	38.4	37.7	38.1
	Median	38.5	35.1	37.5
	SD	4.9	5.7	5.2
	MIN,MAX	30,48	30,47	30,48
	Q1,Q3	35,42	34,44	34,42
	n	15	16	31
	Nmiss	0	0	0

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3.3.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 6	Mean	40.9	40.1	40.5
	Median	41.1	39.4	40.4
	SD	4.5	5.5	4.9
	MIN,MAX	33,51	32,48	32,51
	Q1,Q3	38,44	36,45	37,44
	n	15	13	28
	Nmiss	0	3	3
Calculated BMI (kg/m^2) change V6 baseli	Mean	2.5	1.7	2.1
	Median	2.2	1.6	1.9
	SD	1.6	2.0	1.8
	MIN,MAX	0,5	-2,6	-2,6
	Q1,Q3	1,4	1,3	1,3
	n	15	13	28
	Nmiss	0	3	3

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.3.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and ist change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 9	Mean	38.4	37.1	37.8
	Median	39.6	36.2	38.7
	SD	3.6	6.2	4.9
	MIN,MAX	29,43	29,47	29,47
	Q1,Q3	36,40	32,43	36,40
	n	13	11	24
	Nmiss	2	5	7
Calculated BMI (kg/m^2) change V9 baseli	Mean	-0.1	-1.4	-0.7
	Median	-0.8	-1.3	-0.9
	SD	2.5	2.6	2.6
	MIN,MAX	-5,5	-7,1	-7,5
	Q1,Q3	-1,1	-3,1	-2,1
	n	13	11	24
	Nmiss	2	5	7

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Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.4.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 1 (days)	Mean	88.0	86.7	87.3
	Median	87.0	88.5	88.0
	SD	11.2	14.9	13.0
	MIN,MAX	72,105	60,109	60,109
	Q1,Q3	78,99	77,98	78,99
	n	15	16	31
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	99.1	99.1	99.1
	Median	98.0	99.5	99.0
	SD	7.4	8.1	7.6
	MIN,MAX	91,111	86,111	86,111
	Q1,Q3	92,104	93,107	92,106
	n	15	16	31
	Nmiss	0	0	0

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*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value

Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.4.2 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 3 (days)	Mean	100.5	99.9	100.2
	Median	100.0	100.0	100.0
	SD	7.2	7.8	7.4
	MIN,MAX	92,112	86,111	86,112
	Q1,Q3	93,108	95,108	93,108
	n	15	16	31
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	152.9	142.9	147.7
	Median	144.5	141.0	143.0
	SD	29.1	8.0	21.2
	MIN,MAX	137,252	134,166	134,252
	Q1,Q3	142,149	138,145	141,145
	n	14	15	29
	Nmiss	1	1	2

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Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.4.3 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 5 (days)	Mean	197.4	196.2	196.8
	Median	198.0	195.5	196.5
	SD	4.8	4.4	4.6
	MIN,MAX	189,204	190,206	189,206
	Q1,Q3	195,202	193,198	194,201
	n	14	14	28
	Nmiss	1	2	3
Calculated* Gestation - Visit 6 (days)	Mean	253.1	253.0	253.1
	Median	252.0	254.0	253.5
	SD	3.4	5.9	4.6
	MIN,MAX	248,259	240,260	240,260
	Q1,Q3	251,255	251,256	251,256
	n	15	13	28
	Nmiss	0	3	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.4.4 Gestation by timepoint - Visit 7 Term, Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 7 (days)	Mean	281.6	279.0	280.3
	Median	281.0	279.0	280.0
	SD	5.4	2.4	4.2
	MIN,MAX	275,288	275,281	275,288
	Q1,Q3	278,286	279,281	278,281
	n	5	5	10
	Nmiss	10	11	21
Calculated* Gestation - Visit 8 (days)	Mean	278.2	277.0	277.6
	Median	281.0	280.5	281.0
	SD	10.5	17.7	14.5
	MIN,MAX	260,291	216,294	216,294
	Q1,Q3	273,287	274,287	273,287
	n	15	16	31
	Nmiss	0	0	0

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Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

3.4.5 Gestation by timepoint - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Recorded* Gestation - Visit 8 (days)	Mean	277.4	276.1	276.7
	Median	277.0	278.0	277.0
	SD	10.2	16.5	13.6
	MIN,MAX	260,291	219,290	219,291
	Q1,Q3	272,286	274,286	272,286
	n	15	16	31
	Nmiss	0	0	0
Coded R_gestation - Visit 8 (n(%))	>24 and <=37 WEEKS	0	1 (6.3)	1 (3.2)
	>37 WEEKS	15 (100)	15 (93.8)	30 (96.8)

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*Actual recorded value

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Section 4. Magnetic resonance studies

4.1 Maternal Age at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of patients in substudy-MRI (n)	Yes	30	27	57
Maternal Age at consent (years)	Mean	29.4	30.1	29.7
	Median	29.0	31.0	30.0
	SD	4.5	5.5	5.0
	MIN,MAX	21,37	19,39	19,39
	Q1,Q3	26,33	26,35	26,33
	n	30	27	57
	Nmiss	0	0	0

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Section 4. Magnetic resonance studies

4.2 Previous pregnacy status* PARITY 1 at Baseline - Visit 2 (10-16 Weeks) - Demographics and Lifestyle

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
PARITY1 (n(%))	0	11 (36.7)	11 (40.7)	22 (38.6)
	=>1	19 (63.3)	16 (59.3)	35 (61.4)

N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 24 weeks or more were considered

Section 4. Magnetic resonance studies

4.3.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 2	Mean	38.2	39.4	38.7
	Median	37.5	38.7	38.2
	SD	5.6	4.7	5.2
	MIN,MAX	30,56	31,47	30,56
	Q1,Q3	35,41	36,44	36,42
	n	30	27	57
	Nmiss	0	0	0

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4.3.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 6	Mean	40.3	41.4	40.8
	Median	40.6	40.2	40.4
	SD	5.4	4.3	4.9
	MIN,MAX	32,56	35,48	32,56
	Q1,Q3	37,43	38,45	37,43
	n	29	23	52
	Nmiss	1	4	5
Calculated BMI (kg/m^2) change V6 baseli	Mean	2.1	1.8	2.0
	Median	1.8	1.7	1.8
	SD	1.7	1.7	1.7
	MIN,MAX	-0,7	-2,6	-2,7
	Q1,Q3	1,3	1,3	1,3
	n	29	23	52
	Nmiss	1	4	5

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Section 3. Endothelial function Effect of metformin on flow-mediated dilatation

4.3.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and ist change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 9	Mean	38.0	39.0	38.5
	Median	39.0	38.0	38.8
	SD	4.0	4.6	4.3
	MIN,MAX	29,44	33,49	29,49
	Q1,Q3	35,40	36,40	36,40
	n	23	21	44
	Nmiss	7	6	13
Calculated BMI (kg/m^2) change V9 baseli	Mean	-0.6	-1.0	-0.8
	Median	-0.8	-1.1	-0.9
	SD	2.0	2.3	2.1
	MIN,MAX	-5,3	-7,4	-7,4
	Q1,Q3	-2,1	-2,0	-2,1
	n	23	21	44
	Nmiss	7	6	13

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4.4.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 1 (days)	Mean	89.8	89.1	89.5
	Median	89.0	89.0	89.0
	SD	13.4	11.9	12.6
	MIN,MAX	69,111	60,109	60,111
	Q1,Q3	77,102	84,98	81,99
	n	30	27	57
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	100.5	99.3	99.9
	Median	103.0	100.0	100.0
	SD	10.2	7.9	9.2
	MIN,MAX	78,112	85,111	78,112
	Q1,Q3	91,110	93,107	92,109
	n	30	27	57
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value

Section 4. Magnetic resonance studies

4.4.2 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 3 (days)	Mean	102.6	100.1	101.4
	Median	103.5	100.0	102.0
	SD	8.5	7.7	8.2
	MIN,MAX	87,113	85,112	85,113
	Q1,Q3	93,111	96,109	96,109
	n	30	27	57
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	146.7	144.0	145.4
	Median	145.0	141.0	143.5
	SD	7.8	8.5	8.2
	MIN,MAX	133,164	134,166	133,166
	Q1,Q3	142,151	139,149	140,151
	n	29	27	56
	Nmiss	1	0	1

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4.4.3 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 5 (days)	Mean	196.5	198.1	197.2
	Median	197.5	198.0	198.0
	SD	4.0	4.0	4.0
	MIN,MAX	189,202	190,206	189,206
	Q1,Q3	193,200	195,201	195,200
	n	30	27	57
	Nmiss	0	0	0
Calculated* Gestation - Visit 6 (days)	Mean	253.3	254.7	253.9
	Median	254.0	254.0	254.0
	SD	3.8	4.5	4.1
	MIN,MAX	244,259	243,264	243,264
	Q1,Q3	251,256	252,256	251,256
	n	29	26	55
	Nmiss	1	1	2

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 4. Magnetic resonance studies

4.4.4 Gestation by timepoint - Visit 7 Term, Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 7 (days)	Mean	282.2	280.6	281.5
	Median	282.0	281.0	281.0
	SD	3.4	2.7	3.2
	MIN,MAX	275,288	275,285	275,288
	Q1,Q3	281,285	280,282	280,283
	n	13	10	23
	Nmiss	17	17	34
Calculated* Gestation - Visit 8 (days)	Mean	282.0	279.3	280.7
	Median	283.0	280.0	283.0
	SD	9.7	9.6	9.7
	MIN,MAX	257,294	250,294	250,294
	Q1,Q3	275,289	274,285	275,287
	n	30	27	57
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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4.4.5 Gestation by timepoint - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Recorded* Gestation - Visit 8 (days)	Mean	280.8	278.4	279.7
	Median	281.5	278.0	280.0
	SD	9.4	9.6	9.5
	MIN,MAX	256,294	247,293	247,294
	Q1,Q3	275,287	274,285	275,286
	n	30	27	57
	Nmiss	0	0	0
Coded R_gestation - Visit 8 (n(%))	>24 and <=37 WEEKS	1 (3.3)	1 (3.7)	2 (3.5)
	>37 WEEKS	29 (96.7)	26 (96.3)	55 (96.5)

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Actual recorded value

Section 4. Magnetic resonance studies

4.5.1 Demographic characteristics of neonate

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Baby Gender (n(%))	Male	14 (46.7)	11 (40.7)	25 (43.9)
	Female	16 (53.3)	16 (59.3)	32 (56.1)
Birth weight (g)	Mean	3493.0	3596.1	3541.8
	Median	3450.0	3660.0	3500.0
	SD	512.4	494.7	502.3
	MIN,MAX	2400,4520	2730,4490	2400,4520
	Q1,Q3	3020,3850	3260,3820	3190,3850
	n	30	27	57
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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DOI: 10.3310/eme03070

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4.5.2 Demographic characteristics of neonate (Cont.)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth weight centile	Mean	51.724	63.415	57.262
	Median	52.903	66.692	57.844
	SD	29.619	25.839	28.266
	MIN,MAX	3.34,98.13	8.88,98.51	3.34,98.51
	Q1,Q3	28.70,78.37	39.55,84.52	35.36,82.48
	n	30	27	57
	Nmiss	0	0	0
Split Birth weight Centile (n(%))	>3rd and <=5th	1 (3.3)	0	1 (1.8)
	>5th and <=10th	3 (10.0)	1 (3.7)	4 (7.0)
	>10th and <=90th	22 (73.3)	20 (74.1)	42 (73.7)
	>90th and <=95th	1 (3.3)	3 (11.1)	4 (7.0)
	>95th and <=97th	2 (6.7)	1 (3.7)	3 (5.3)
	>97th	1 (3.3)	2 (7.4)	3 (5.3)

Section 4. Magnetic resonance studies

4.6.1 Anthropometry of neonate - Ponderal index#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Baby ponderal index*-V8	Mean	3.44	2.60	3.04
	Median	2.42	2.57	2.54
	SD	4.59	0.32	3.32
	MIN,MAX	2.1,24.9	1.9,3.2	1.9,24.9
	Q1,Q3	2.3,2.6	2.5,2.8	2.4,2.8
	n	24	22	46
	Nmiss	6	5	11
Baby ponderal index*-V9	Mean	2.61	2.56	2.59
	Median	2.53	2.60	2.56
	SD	0.26	0.26	0.26
	MIN,MAX	2.1,3.2	2.2,2.9	2.1,3.2
	Q1,Q3	2.4,2.8	2.3,2.8	2.4,2.8
	n	24	22	46
	Nmiss	6	5	11

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
Ponderal index was calculated using the following formula: (100(baby_weight_in_g))/((baby_lenght_in_cm)^3)
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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4.6.2 Anthropometry of neonate - Baby Skinfold Triceps*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Baby Skinfold Triceps(mm)-V8	Mean	11.38	8.30	9.84
	Median	8.00	8.00	8.00
	SD	18.08	2.46	12.84
	MIN,MAX	4.5,90.0	5.2,14.0	4.5,90.0
	Q1,Q3	6.0,9.0	6.5,10.0	6.0,9.0
	n	21	21	42
	Nmiss	9	6	15
Baby Skinfold Triceps(mm)-V9	Mean	12.87	11.00	12.00
	Median	12.00	10.70	11.00
	SD	3.92	3.68	3.88
	MIN,MAX	7.5,19.0	6.0,24.0	6.0,24.0
	Q1,Q3	9.5,17.0	10.0,12.0	10.0,14.0
	n	23	20	43
	Nmiss	7	7	14

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 4. Magnetic resonance studies

4.6.3 Anthropometry of neonate - Baby Skinfold Subscapular*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Baby Skinfold Subscapular(mm)-V8	Mean	10.06	7.11	8.59
	Median	7.00	7.00	7.00
	SD	13.94	2.33	9.98
	MIN,MAX	4.5,70.0	4.0,12.0	4.0,70.0
	Q1,Q3	5.0,8.0	6.0,8.0	5.0,8.0
	n	21	21	42
	Nmiss	9	6	15
Baby Skinfold Subscapular(mm)-V9	Mean	9.80	9.68	9.74
	Median	9.00	9.00	9.00
	SD	3.18	2.89	3.01
	MIN,MAX	6.0,19.0	7.0,20.0	6.0,20.0
	Q1,Q3	7.5,11.5	8.0,11.0	8.0,11.0
	n	22	20	42
	Nmiss	8	7	15

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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DOI: 10.3310/eme03070

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4.6.4 Anthropometry of neonate - Baby Fat %*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
BABY FAT (%)-V8	Mean	12.53	12.63	12.58
	Median	10.90	12.30	12.30
	SD	5.68	4.27	4.90
	MIN,MAX	2.1,24.3	5.7,19.6	2.1,24.3
	Q1,Q3	8.1,17.1	10.0,15.9	8.5,16.1
	n	15	17	32
	Nmiss	15	10	25
BABY FAT (%)-V9	Mean	25.80	23.73	24.85
	Median	25.70	24.50	25.30
	SD	6.02	6.01	6.02
	MIN,MAX	15.1,41.6	12.1,32.3	12.1,41.6
	Q1,Q3	22.2,29.0	19.6,27.9	20.9,29.0
	n	21	18	39
	Nmiss	9	9	18

Section 5. Saliva Samples

5.1.1 Maternal Age at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
number of patients in substudy-SALIVA (n)	Yes	121	114	235
Maternal Age at consent (years)	Mean	29.9	29.1	29.5
	Median	30.0	29.0	29.0
	SD	5.0	5.6	5.3
	MIN,MAX	20,41	18,42	18,42
	Q1,Q3	26,34	25,33	25,33
	n	121	114	235
	Nmiss	0	0	0

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Section 5. Saliva Samples

5.1.2 Maternal smoking Status at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Smoking Status (n(%))	ACTIVE	9 (7.4)	15 (13.2)	24 (10.2)
	PREVIOUSLY	6 (5.0)	5 (4.4)	11 (4.7)
	NOT SMOKING	106 (87.6)	94 (82.5)	200 (85.1)

Section 5. Saliva Samples

5.1.3 Maternal Education

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Educational Qualifications (n(%))	No formal qualifications	7 (5.8)	5 (4.4)	12 (5.1)
	Entry level certification/foundation diploma	3 (2.5)	6 (5.3)	9 (3.8)
	GCSE, Standard grade, "O" grades	31 (25.6)	20 (17.5)	51 (21.7)
	A level, A/S level, Highers or BTEC Dip/Cert.	29 (24.0)	15 (13.2)	44 (18.7)
	Cert. higher Education, City & Guilds	9 (7.4)	9 (7.9)	18 (7.7)
	Diploma HE/FE or HND/HNC	11 (9.1)	18 (15.8)	29 (12.3)
	Graduate certificate or Diploma	3 (2.5)	7 (6.1)	10 (4.3)
	Degree	18 (14.9)	27 (23.7)	45 (19.1)
	Professional Qualification	3 (2.5)	2 (1.8)	5 (2.1)
	PGCE/Postgraduate certificate or Diploma, Masters. Doctorate	7 (5.8)	5 (4.4)	12 (5.1)
Educational Qualifications coded (n(%))	None	7 (5.8)	5 (4.4)	12 (5.1)
	School up to 16 years	34 (28.1)	26 (22.8)	60 (25.5)
	School 16 to 18 years	38 (31.4)	24 (21.1)	62 (26.4)
	College or Uni degree or Higher	42 (34.7)	59 (51.8)	101 (43.0)

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5.2 Previous pregnacy status* PARITY 1 at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
PARITY1 (n(%))	0	50 (41.3)	52 (45.6)	102 (43.4)
	=>1	71 (58.7)	62 (54.4)	133 (56.6)

N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 24 weeks or more were considered

Section 5. Saliva Samples

5.3.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 2	Mean	36.9	37.5	37.2
	Median	36.1	36.8	36.3
	SD	5.0	5.2	5.1
	MIN,MAX	30,53	30,57	30,57
	Q1,Q3	33,40	34,41	33,40
	n	121	114	235
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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5.3.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 6	Mean	39.5	40.1	39.8
	Median	38.7	39.2	38.8
	SD	5.2	5.1	5.2
	MIN,MAX	32,54	32,55	32,55
	Q1,Q3	35,42	36,43	36,43
	n	101	86	187
	Nmiss	20	28	48
Calculated BMI (kg/m^2) change V6 baseli	Mean	2.8	2.3	2.5
	Median	2.6	2.2	2.5
	SD	1.9	2.1	2.0
	MIN,MAX	-3,7	-2,12	-3,12
	Q1,Q3	2,4	1,3	1,3
	n	101	86	187
	Nmiss	20	28	48

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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5.3.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 9	Mean	36.7	38.1	37.4
	Median	36.4	37.4	36.9
	SD	4.5	5.8	5.2
	MIN,MAX	29,52	29,61	29,61
	Q1,Q3	34,40	33,42	33,40
	n	83	84	167
	Nmiss	38	30	68
Calculated BMI (kg/m^2) change V9 baseli	Mean	0.3	0.2	0.2
	Median	-0.0	-0.2	-0.1
	SD	2.1	3.5	2.9
	MIN,MAX	-5,5	-5,25	-5,25
	Q1,Q3	-1,2	-1,1	-1,1
	n	83	84	167
	Nmiss	38	30	68

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 5. Saliva Samples

5.4.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 1 (days)	Mean	86.7	86.4	86.5
	Median	86.0	88.0	88.0
	SD	13.3	13.7	13.5
	MIN,MAX	51,111	51,110	51,111
	Q1,Q3	80,96	82,95	80,96
	n	121	114	235
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	99.7	99.9	99.8
	Median	102.0	100.0	101.0
	SD	8.8	7.7	8.2
	MIN,MAX	74,112	75,112	74,112
	Q1,Q3	93,107	94,107	93,107
	n	121	114	235
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value

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5.4.2 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 3 (days)	Mean	101.5	101.4	101.5
	Median	103.0	102.0	102.0
	SD	8.3	6.9	7.6
	MIN,MAX	84,118	85,112	84,118
	Q1,Q3	95,108	97,108	96,108
	n	121	114	235
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	142.5	140.2	141.4
	Median	141.0	140.0	141.0
	SD	11.0	10.0	10.6
	MIN,MAX	125,198	114,200	114,200
	Q1,Q3	137,146	134,143	137,145
	n	116	111	227
	Nmiss	5	3	8

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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5.4.3 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 5 (days)	Mean	197.6	197.7	197.6
	Median	198.0	198.0	198.0
	SD	4.8	5.5	5.1
	MIN,MAX	185,217	167,217	167,217
	Q1,Q3	195,200	196,201	195,200
	n	117	106	223
	Nmiss	4	8	12
Calculated* Gestation - Visit 6 (days)	Mean	253.1	253.0	253.1
	Median	253.0	253.0	253.0
	SD	4.3	5.0	4.6
	MIN,MAX	241,263	234,264	234,264
	Q1,Q3	251,256	250,256	251,256
	n	104	93	197
	Nmiss	17	21	38

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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5.4.4 Gestation by timepoint - Visit 7 Term, Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 7 (days)	Mean	279.1	280.2	279.6
	Median	276.0	278.0	278.0
	SD	17.9	23.2	20.6
	MIN,MAX	262,414	250,419	250,419
	Q1,Q3	273,281	274,280	274,280
	n	71	68	139
	Nmiss	50	46	96
Calculated* Gestation - Visit 8 (days)	Mean	281.9	276.1	279.1
	Median	281.0	280.0	281.0
	SD	16.8	21.2	19.2
	MIN,MAX	209,375	143,306	143,375
	Q1,Q3	274,289	271,286	273,287
	n	120	112	232
	Nmiss	1	2	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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5.4.5 Gestation by timepoint - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Recorded* Gestation - Visit 8 (days)	Mean	277.6	275.0	276.4
	Median	278.0	278.0	278.0
	SD	11.8	18.1	15.2
	MIN,MAX	211,298	143,297	143,298
	Q1,Q3	272,287	271,285	271,286
	n	121	111	232
	Nmiss	0	3	3
Coded R_gestation - Visit 8 (n(%))	Missing	0	3	3
	<= 24 WEEKS	0	1 (0.9)	1 (0.4)
	>24 and <=37 WEEKS	5 (4.1)	10 (9.0)	15 (6.5)
	>37 WEEKS	116 (95.9)	100 (90.1)	216 (93.1)

Section 5. Saliva Samples

5.5.1.1 Saliva Free Cortisol (SFC) at Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		----------Allocated_Intervention----------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
SFC V2 BEDTIME	Mean	2.2314	1.9952	2.1167
	Median	0.9690	1.1340	1.0750
	SD	8.0296	2.3755	5.9796
	MIN,MAX	0.358,77.820	0.338,12.481	0.338,77.820
	Q1,Q3	0.680,1.320	0.784,1.983	0.732,1.570
	n	107	101	208
	Nmiss	0	0	0
SFC V2 WAKING	Mean	9.0267	6.3600	7.7318
	Median	5.8280	5.6950	5.7775
	SD	24.5826	3.8566	17.8443
	MIN,MAX	0.638,258.56	0.714,19.996	0.638,258.56
	Q1,Q3	4.605,8.363	3.731,9.012	4.160,8.657
	n	107	101	208
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 5. Saliva Samples

5.5.1.2 Saliva Free Cortisol (SFC) at Visit 2 Consent/Baseline (10-16 Weeks) - Difference Bedtime-Awake

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
SFC V2 DIFF bedtime to awake	Mean	-6.7953	-4.3649	-5.6151
	Median	-4.8610	-4.5830	-4.6875
	SD	22.4869	5.1146	16.5244
	MIN,MAX	-227.2,53.343	-17.27,11.642	-227.2,53.343
	Q1,Q3	-7.169,-3.321	-7.489,-2.450	-7.181,-2.953
	n	107	101	208
	Nmiss	0	0	0

Section 5. Saliva Samples

5.5.2.1 Saliva Free Cortisol (SFC) at Visit 5 (28 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
SFC V5 BEDTIME	Mean	3.1661	2.0399	2.5805
	Median	1.9545	1.7570	1.8555
	SD	3.9816	1.5810	3.0222
	MIN,MAX	1.120,23.885	0.838,12.126	0.838,23.885
	Q1,Q3	1.645,2.835	1.457,2.082	1.531,2.353
	n	48	52	100
	Nmiss	0	1	1
SFC V5 WAKING	Mean	8.6792	9.2571	8.9797
	Median	8.7065	8.4330	8.5250
	SD	6.9342	4.2930	5.6926
	MIN,MAX	0.986,47.022	2.401,26.293	0.986,47.022
	Q1,Q3	4.221,10.426	6.325,11.388	6.023,11.271
	n	48	52	100
	Nmiss	0	1	1

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Section 5. Saliva Samples

5.5.2.2 Saliva Free Cortisol (SFC) at Visit 5 (28 Weeks)- Difference Bedtime-Awake

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
SFC V5 DIFF bedtime to awake	Mean	-5.5131	-7.2172	-6.3992
	Median	-6.2640	-6.6210	-6.4945
	SD	7.8224	3.7307	6.0788
	MIN,MAX	-43.79,14.895	-18.29,-0.540	-43.79,14.895
	Q1,Q3	-8.158,-2.400	-9.697,-4.488	-8.984,-4.175
	n	48	52	100
	Nmiss	0	1	1

Section 5. Saliva Samples

5.5.3.1 Saliva Free Cortisol (SFC) at Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
SFC V6 BEDTIME	Mean	3.3966	2.9771	3.1732
	Median	2.5890	2.3480	2.3720
	SD	3.1531	1.8249	2.5250
	MIN,MAX	1.562,20.063	1.500,8.688	1.500,20.063
	Q1,Q3	2.084,3.361	2.071,2.975	2.078,3.163
	n	36	41	77
	Nmiss	0	0	0
SFC V6 WAKING	Mean	8.8989	8.7360	8.8122
	Median	8.2175	7.9910	8.2100
	SD	4.1708	4.8077	4.4926
	MIN,MAX	2.948,21.496	1.918,32.084	1.918,32.084
	Q1,Q3	5.940,10.071	6.011,10.407	6.008,10.283
	n	36	41	77
	Nmiss	0	0	0

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Section 5. Saliva Samples

5.5.3.2 Saliva Free Cortisol (SFC) at Visit 6 (36 Weeks)- Difference Bedtime-Awake

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
SFC V6 DIFF bedtime to awake	Mean	-5.5023	-5.7590	-5.6390
	Median	-4.8690	-5.5540	-5.3730
	SD	3.6587	5.6015	4.7640
	MIN,MAX	-14.23,0.373	-29.06,6.770	-29.06,6.770
	Q1,Q3	-7.566,-2.889	-7.568,-3.665	-7.568,-3.300
	n	36	41	77
	Nmiss	0	0	0

Section 5. Saliva Samples

5.5.4 Saliva Free Cortisol (SFC) Differences Bedtime-Awake Statistical Analysis by timepoint

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
SA_2V_DIF_log - itt	5.484	0.0170	107	5.507	0.0173	101	0.023	-0.022	0.069	1.031	0.3111
SA_5V_DIF_log - itt	5.495	0.0040	48	5.489	0.0037	52	-0.006	-0.016	0.004	1.509	0.2223
SA_6V_DIF_log - itt	5.499	0.0036	36	5.498	0.0032	41	-0.001	-0.010	0.008	0.080	0.7780

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Summary statistics are presented in tables 5.5.1 to 5.5.3 of this report
Outcome analysed using a linear regression model, ajusted by BMI band. Significance level set at p<0.05
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_5_5_SALIVA_LABS_ANALYSIS.lst'
All parameters shown normal or near-normal behavior

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Section 6. Placental biopsies

6.1.1 Maternal Age at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of patients in substudy-PLACENTATISSUE (n)	Yes	64	61	125
Maternal Age at consent (years)	Mean	29.2	29.7	29.4
	Median	29.0	30.0	29.0
	SD	5.5	5.3	5.4
	MIN,MAX	21,41	19,40	19,41
	Q1,Q3	24,33	25,34	25,34
	n	64	61	125
	Nmiss	0	0	0

Section 6. Placental biopsies

6.1.2 Maternal smoking Status at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Smoking Status (n(%))	ACTIVE	7 (10.9)	10 (16.4)	17 (13.6)
	PREVIOUSLY	2 (3.1)	2 (3.3)	4 (3.2)
	NOT SMOKING	55 (85.9)	49 (80.3)	104 (83.2)

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Section 6. Placental biopsies

6.1.3 Maternal Education

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Educational Qualifications (n(%))	No formal qualifications	4 (6.3)	4 (6.6)	8 (6.4)
	Entry level certification/foundation diploma	1 (1.6)	3 (4.9)	4 (3.2)
	GCSE, Standard grade, "O" grades	15 (23.4)	6 (9.8)	21 (16.8)
	A level, A/S level, Highers or BTEC Dip/Cert.	13 (20.3)	7 (11.5)	20 (16.0)
	Cert. higher Education, City & Guilds	5 (7.8)	6 (9.8)	11 (8.8)
	Diploma HE/FE or HND/HNC	9 (14.1)	11 (18.0)	20 (16.0)
	Graduate certificate or Diploma	2 (3.1)	4 (6.6)	6 (4.8)
	Degree	12 (18.8)	19 (31.1)	31 (24.8)
	PGCE/Postgraduate certificate or Diploma, Masters. Doctorate	3 (4.7)	1 (1.6)	4 (3.2)
Educational Qualifications coded (n(%))	None	4 (6.3)	4 (6.6)	8 (6.4)
	School up to 16 years	16 (25.0)	9 (14.8)	25 (20.0)
	School 16 to 18 years	18 (28.1)	13 (21.3)	31 (24.8)
	College or Uni degree or Higher	26 (40.6)	35 (57.4)	61 (48.8)

Section 6. Placental biopsies

6.2 Previous pregnacy status* PARITY 1 at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
PARITY1 (n(%))	0	22 (34.4)	27 (44.3)	49 (39.2)
	=>1	42 (65.6)	34 (55.7)	76 (60.8)

N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 24 weeks or more were considered

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Section 6. Placental biopsies

6.3.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 2	Mean	37.0	38.3	37.6
	Median	36.1	38.2	36.7
	SD	5.2	5.3	5.2
	MIN,MAX	30,53	30,51	30,53
	Q1,Q3	33,41	34,42	33,41
	n	64	61	125
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 6. Placental biopsies

6.3.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 6	Mean	39.1	40.3	39.7
	Median	37.8	39.4	38.9
	SD	4.8	5.1	5.0
	MIN,MAX	31,53	32,51	31,53
	Q1,Q3	36,42	37,45	36,43
	n	55	55	110
	Nmiss	9	6	15
Calculated BMI (kg/m^2) change V6 baseli	Mean	2.2	2.0	2.1
	Median	2.2	2.0	2.1
	SD	1.6	1.8	1.7
	MIN,MAX	-3,6	-2,7	-3,7
	Q1,Q3	2,3	1,3	1,3
	n	55	55	110
	Nmiss	9	6	15

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 6. Placental biopsies

6.3.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and ist change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 9	Mean	36.9	38.0	37.5
	Median	36.1	37.3	37.0
	SD	4.6	6.2	5.5
	MIN,MAX	28,48	29,61	28,61
	Q1,Q3	34,40	33,42	34,40
	n	48	53	101
	Nmiss	16	8	24
Calculated BMI (kg/m^2) change V9 baseli	Mean	-0.3	-0.1	-0.2
	Median	-0.6	-0.7	-0.6
	SD	2.3	4.2	3.4
	MIN,MAX	-5,5	-7,25	-7,25
	Q1,Q3	-2,1	-2,1	-2,1
	n	48	53	101
	Nmiss	16	8	24

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 6. Placental biopsies

6.4.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 1 (days)	Mean	83.8	84.5	84.1
	Median	84.0	85.0	85.0
	SD	13.9	14.4	14.1
	MIN,MAX	51,109	51,109	51,109
	Q1,Q3	74,95	76,94	74,94
	n	64	61	125
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	100.1	100.0	100.0
	Median	103.5	100.0	102.0
	SD	9.6	7.7	8.7
	MIN,MAX	71,112	82,111	71,112
	Q1,Q3	95,108	94,107	94,108
	n	64	61	125
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value

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Section 6. Placental biopsies

6.4.2 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 3 (days)	Mean	102.2	101.6	101.9
	Median	105.5	103.0	104.0
	SD	8.1	7.1	7.6
	MIN,MAX	84,112	85,112	84,112
	Q1,Q3	97,108	96,108	97,108
	n	64	61	125
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	142.8	138.9	140.8
	Median	140.0	140.0	140.0
	SD	19.7	6.7	14.8
	MIN,MAX	108,252	126,166	108,252
	Q1,Q3	133,145	134,142	133,144
	n	61	61	122
	Nmiss	3	0	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 6. Placental biopsies

6.4.3 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 5 (days)	Mean	198.2	197.6	197.9
	Median	198.0	197.0	197.0
	SD	10.6	5.5	8.5
	MIN,MAX	189,275	167,208	167,275
	Q1,Q3	195,200	196,201	196,200
	n	63	60	123
	Nmiss	1	1	2
Calculated* Gestation - Visit 6 (days)	Mean	253.9	252.8	253.3
	Median	254.0	253.0	253.0
	SD	3.6	3.8	3.7
	MIN,MAX	246,263	240,261	240,263
	Q1,Q3	252,256	251,254	251,256
	n	58	57	115
	Nmiss	6	4	10

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 6. Placental biopsies

6.4.4 Gestation by timepoint - Visit 7 Term, Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 7 (days)	Mean	277.2	279.4	278.3
	Median	276.0	276.5	276.0
	SD	7.2	19.6	14.6
	MIN,MAX	256,298	263,393	256,393
	Q1,Q3	273,282	273,280	273,281
	n	39	38	77
	Nmiss	25	23	48
Calculated* Gestation - Visit 8 (days)	Mean	279.3	278.7	279.0
	Median	279.5	280.0	280.0
	SD	10.7	9.6	10.1
	MIN,MAX	257,305	254,298	254,305
	Q1,Q3	273,288	271,285	272,287
	n	64	61	125
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 6. Placental biopsies

6.4.5 Gestation by timepoint - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Recorded* Gestation - Visit 8 (days)	Mean	277.5	277.6	277.6
	Median	277.0	278.0	277.0
	SD	9.4	9.6	9.5
	MIN,MAX	256,294	253,297	253,297
	Q1,Q3	272,285	271,284	271,284
	n	64	61	125
	Nmiss	0	0	0
Coded R_gestation - Visit 8 (n(%))	>24 and <=37 WEEKS	2 (3.1)	3 (4.9)	5 (4.0)
	>37 WEEKS	62 (96.9)	58 (95.1)	120 (96.0)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Actual recorded value

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Section 6. Placental biopsies

6.5.1 Delivery Details - alive births

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Delivery Method (n(%))	Spontaneous vaginal delivery	34 (53.1)	34 (55.7)	68 (54.4)
	LSCS in labour	10 (15.6)	7 (11.5)	17 (13.6)
	LSCS pre labour	17 (26.6)	13 (21.3)	30 (24.0)
	Forceps/ventouse	3 (4.7)	7 (11.5)	10 (8.0)
C-SECTION index pregnancy (n(%))	Yes	27 (42.2)	20 (32.8)	47 (37.6)
	No	37 (57.8)	41 (67.2)	78 (62.4)
Primary C-SECTION in index pregancy (n(%))	Yes	15 (23.4)	10 (16.4)	25 (20.0)
	No	49 (76.6)	51 (83.6)	100 (80.0)

Section 6. Placental biopsies

6.5.2 Delivery Outcome

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Birth Outcome (n(%))	Live Birth	64 (100)	61 (100)	125 (100)
Baby Gender (n(%))	Male	31 (48.4)	34 (55.7)	65 (52.0)
	Female	33 (51.6)	27 (44.3)	60 (48.0)

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Section 6. Placental biopsies

6.6.1 GR_NR3C

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
GR_NR3C1	Mean	0.8404	0.8088	0.8250
	Median	0.7729	0.7208	0.7628
	SD	0.4924	0.4367	0.4644
	MIN,MAX	0.110,2.887	0.109,2.452	0.109,2.887
	Q1,Q3	0.527,0.979	0.529,1.055	0.529,0.995
	n	64	61	125
	Nmiss	0	0	0

Section 6. Placental biopsies

6.6.2 HSD1 and HSD2

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------*Allocated_Intervention*---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
HSD1	Mean	2.2783	2.4612	2.3675
	Median	1.0648	1.3578	1.3066
	SD	3.0948	3.2035	3.1369
	MIN,MAX	0.037,18.376	0.067,17.556	0.037,18.376
	Q1,Q3	0.531,2.866	0.597,3.057	0.562,2.911
	n	64	61	125
	Nmiss	0	0	0
HSD2	Mean	4.2637	3.3163	3.8014
	Median	1.4368	1.7528	1.6229
	SD	7.2764	5.3983	6.4208
	MIN,MAX	0.234,43.101	0.145,29.653	0.145,43.101
	Q1,Q3	0.873,4.040	0.915,2.775	0.878,3.050
	n	64	61	125
	Nmiss	0	0	0

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Section 6. Placental biopsies

6.6.3 gr_nr3c1, hsd2 and hsd2 Statistical Analysis

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

	--- Placebo ---			--- Metformin ---							
Parameter(s)	*Estimated Mean*	*SE*	*n*	*Estimated Mean*	*SE*	*n*	*Estimated Mean Difference**	*Estimated Mean Difference Lower CI**	*Estimated Mean Difference Upper CI**	*Statistic (t-test)*	*p-value*
gr_nr3c1_log - itt	-0.299	0.0775	64	-0.324	0.0792	61	-0.025	-0.236	0.187	0.053	0.8176
hsd1_log - itt	0.056	0.1666	64	0.189	0.1705	61	0.133	-0.322	0.589	0.336	0.5633
hsd2_log - itt	0.590	0.1367	64	0.433	0.1398	61	-0.157	-0.531	0.216	0.696	0.4059

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Summary statistics are presented in tables 6.6.1 to 6.6.2 of this report
Outcome analysed using a linear regression model, ajusted by BMI band and c-section index pregnancy (6.5.1). Significance level set at $p<0.05$
Estimated mean represents the adjusted means of the log transformed variable by allocated treatment,
SE represents standard error of the estimated log transformed means and N represents number of observations
*Represents the difference between estimated log transformed means and CI Represents the 95% confidence interval
Calculations and detailed analysis are presented in study file 'Empowar_6_6_PLACENTA_LABS_ANALYSIS.lst'
All parameters shown normal or near-normal behavior

Section 7. Myometrial biopsies - Myometrial contractility

7.1.1 Maternal Age at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of patients in substudy-Myo_cont (n)	Yes	2	6	8
Maternal Age at consent (years)	Mean	34.5	27.7	29.4
	Median	34.5	28.0	29.5
	SD	7.8	4.3	5.6
	MIN,MAX	29,40	23,33	23,40
	Q1,Q3	29,40	23,31	25,32
	n	2	6	8
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

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Section 7. Myometrial biopsies - Myometrial contractility

7.1.2 Previous pregnacy status* PARITY 1 at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
PARITY1 (n(%))	0	0	4 (66.7)	4 (50.0)
	=>1	2 (100)	2 (33.3)	4 (50.0)

N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 24 weeks or more were considered

Section 7. Myometrial biopsies - Myometrial contractility

7.1.3.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*#

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 2	Mean	37.6	38.1	38.0
	Median	37.6	38.2	38.2
	SD	7.1	3.7	4.1
	MIN,MAX	33,43	32,43	32,43
	Q1,Q3	33,43	36,41	34,42
	n	2	6	8
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
#Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

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Section 7. Myometrial biopsies - Myometrial contractility

7.1.3.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 6	Mean	37.5	41.0	40.5
	Median	37.5	41.4	40.4
	SD	.	3.7	3.6
	MIN,MAX	37,37	35,45	35,45
	Q1,Q3	37,37	40,44	37,44
	n	1	6	7
	Nmiss	1	0	1
Calculated BMI (kg/m^2) change V6 baseli	Mean	4.8	3.0	3.2
	Median	4.8	2.2	2.2
	SD	.	3.1	2.9
	MIN,MAX	5,5	-1,7	-1,7
	Q1,Q3	5,5	1,6	1,6
	n	1	6	7
	Nmiss	1	0	1

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Myometrial biopsies - Myometrial contractility

7.1.3.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and ist change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 9	Mean	39.1	39.3	39.3
	Median	39.1	41.6	41.6
	SD	6.8	5.5	5.3
	MIN,MAX	34,44	30,44	30,44
	Q1,Q3	34,44	38,43	34,44
	n	2	5	7
	Nmiss	0	1	1
Calculated BMI (kg/m^2) change V9 baseli	Mean	1.4	1.5	1.5
	Median	1.4	-1.1	1.2
	SD	0.3	5.2	4.2
	MIN,MAX	1,2	-3,8	-3,8
	Q1,Q3	1,2	-2,6	-2,6
	n	2	5	7
	Nmiss	0	1	1

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

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Section 7. Myometrial biopsies - Myometrial contractility

7.1.4.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 1 (days)	Mean	62.0	79.0	74.8
	Median	62.0	78.5	74.5
	SD	15.6	10.7	13.4
	MIN,MAX	51,73	68,97	51,97
	Q1,Q3	51,73	69,83	69,82
	n	2	6	8
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	90.5	92.5	92.0
	Median	90.5	95.5	95.0
	SD	6.4	5.9	5.6
	MIN,MAX	86,95	82,97	82,97
	Q1,Q3	86,95	89,96	88,96
	n	2	6	8
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value

Section 7. Myometrial biopsies - Myometrial contractility

7.1.4.2 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 3 (days)	Mean	93.5	100.0	98.4
	Median	93.5	98.0	97.5
	SD	4.9	8.4	7.9
	MIN,MAX	90,97	89,113	89,113
	Q1,Q3	90,97	96,106	93,102
	n	2	6	8
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	138.0	137.0	137.3
	Median	138.0	135.0	135.0
	SD	17.0	9.4	10.2
	MIN,MAX	126,150	126,148	126,150
	Q1,Q3	126,150	130,148	128,148
	n	2	6	8
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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Section 7. Myometrial biopsies - Myometrial contractility

7.1.4.3 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 5 (days)	Mean	195.0	193.3	193.8
	Median	195.0	196.0	195.5
	SD	0.0	14.1	12.0
	MIN,MAX	195,195	167,210	167,210
	Q1,Q3	195,195	194,197	195,197
	n	2	6	8
	Nmiss	0	0	0
Calculated* Gestation - Visit 6 (days)	Mean	254.0	255.7	255.4
	Median	254.0	252.5	253.0
	SD	.	6.0	5.5
	MIN,MAX	254,254	251,266	251,266
	Q1,Q3	254,254	252,260	252,260
	n	1	6	7
	Nmiss	1	0	1

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 7. Myometrial biopsies - Myometrial contractility

7.1.4.4 Gestation by timepoint - Visit 7 Term, Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 7 (days)	Mean	275.0	393.0	334.0
	Median	275.0	393.0	334.0
	SD	.	.	83.4
	MIN,MAX	275,275	393,393	275,393
	Q1,Q3	275,275	393,393	275,393
	n	1	1	2
	Nmiss	1	5	6
Calculated* Gestation - Visit 8 (days)	Mean	274.5	275.8	275.5
	Median	274.5	272.5	273.5
	SD	0.7	7.9	6.7
	MIN,MAX	274,275	270,291	270,291
	Q1,Q3	274,275	271,278	272,277
	n	2	6	8
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*These calculations rely on the accuracy of the recorded date of visit

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Section 7. Myometrial biopsies - Myometrial contractility

7.1.4.5 Gestation by timepoint - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Recorded* Gestation - Visit 8 (days)	Mean	274.0	272.5	272.9
	Median	274.0	271.0	272.5
	SD	1.4	3.7	3.2
	MIN,MAX	273,275	269,278	269,278
	Q1,Q3	273,275	270,276	270,276
	n	2	6	8
	Nmiss	0	0	0
Coded R_gestation - Visit 8 (n(%))	>37 WEEKS	2 (100)	6 (100)	8 (100)

Section 7. Myometrial biopsies - Myometrial contractility

7.1.5 Delivery Details - alive births

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Delivery Method (n(%))	Spontaneous vaginal delivery	0	1 (16.7)	1 (12.5)
	LSCS in labour	0	1 (16.7)	1 (12.5)
	LSCS pre labour	2 (100)	3 (50.0)	5 (62.5)
	Forceps/ventouse	0	1 (16.7)	1 (12.5)
C-SECTION index pregnancy (n(%))	Yes	2 (100)	4 (66.7)	6 (75.0)
	No	0	2 (33.3)	2 (25.0)
Primary C-SECTION in index pregancy (n(%))	Yes	0	3 (50.0)	3 (37.5)
	No	2 (100)	3 (50.0)	5 (62.5)

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Section 7. Myometrial biopsies - Glycogen storage

7.2.1 Maternal Age at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Number of patients in substudy-Gly_sto (n)	Yes	17	11	28
Maternal Age at consent (years)	Mean	29.8	30.0	29.9
	Median	30.0	30.0	30.0
	SD	5.8	4.7	5.3
	MIN,MAX	20,40	23,36	20,40
	Q1,Q3	26,34	27,35	27,35
	n	17	11	28
	Nmiss	0	0	0

Section 7. Myometrial biopsies - Glycogen storage

7.2.2 Previous pregnacy status* PARITY 1 at Baseline - Visit 2 (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
PARITY1 (n(%))	0	6 (35.3)	4 (36.4)	10 (35.7)
	=>1	11 (64.7)	7 (63.6)	18 (64.3)

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N = number of patients randomised, n = number of observations

*Only pregnacies lasting at least 24 weeks or more were considered

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Section 7. Myometrial biopsies - Glycogen storage

7.2.3.1 Maternal Calculated BMI at Visit 2 Consent/Baseline (10-16 Weeks)*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 2	Mean	37.5	40.6	38.7
	Median	37.5	41.1	39.2
	SD	4.6	4.2	4.6
	MIN,MAX	31,45	32,47	31,47
	Q1,Q3	33,42	37,44	34,43
	n	17	11	28
	Nmiss	0	0	0

Section 7. Myometrial biopsies - Glycogen storage

7.2.3.2 Maternal Calculated BMI at Visit 6 (36 Weeks) and its change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 6	Mean	39.4	42.7	40.6
	Median	38.1	42.5	39.8
	SD	4.2	4.8	4.6
	MIN,MAX	34,47	35,51	34,51
	Q1,Q3	36,43	40,45	37,44
	n	16	9	25
	Nmiss	1	2	3
Calculated BMI (kg/m^2) change V6 baseli	Mean	2.1	2.1	2.1
	Median	2.0	2.0	2.0
	SD	1.9	2.5	2.1
	MIN,MAX	-3,5	-2,6	-3,6
	Q1,Q3	2,3	1,2	1,3
	n	16	9	25
	Nmiss	1	2	3

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Data have been checked, innacuracies happened at time and point
of recording and there are not other sources for further checks

By: Aryelly Rodriguez - ECTU Statistician

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Section 7. Myometrial biopsies - Glycogen storage

7.2.3.3 Maternal Calculated BMI at Visit 9 (Final 3 months postnatal) and ist change from baseline*

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated BMI (kg/m^2) at Visit 9	Mean	37.5	39.2	38.1
	Median	37.7	40.1	38.5
	SD	5.0	4.0	4.7
	MIN,MAX	29,47	30,44	29,47
	Q1,Q3	34,41	38,42	34,41
	n	17	8	25
	Nmiss	0	3	3
Calculated BMI (kg/m^2) change V9 baseli	Mean	0.0	-1.6	-0.5
	Median	-0.4	-1.2	-0.5
	SD	2.3	2.7	2.5
	MIN,MAX	-4,5	-7,1	-7,5
	Q1,Q3	-2,1	-3,0	-2,1
	n	17	8	25
	Nmiss	0	3	3

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*Data have been checked, innacuracies happened at time and point of recording and there are not other sources for further checks

Section 7. Myometrial biopsies - Glycogen storage

7.2.4.1 Gestation by timepoint - Visit 1 Screening (10-16 Weeks), Visit 2 Consent/Baseline (10-16 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 1 (days)	Mean	81.1	86.5	83.3
	Median	83.0	87.0	84.0
	SD	14.0	13.1	13.7
	MIN,MAX	51,107	68,109	51,109
	Q1,Q3	72,88	76,96	73,94
	n	17	11	28
	Nmiss	0	0	0
Recorded# Gestation - Visit 2 (days)	Mean	97.9	99.5	98.5
	Median	95.0	101.0	98.5
	SD	9.2	9.4	9.1
	MIN,MAX	84,112	82,111	82,112
	Q1,Q3	92,105	92,108	92,107
	n	17	11	28
	Nmiss	0	0	0

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

#Actual recorded value

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Section 7. Myometrial biopsies - Glycogen storage

7.2.4.2 Gestation by timepoint - Visit 3 Randomisation (10-16 Weeks), Visit 4 (18-20 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 3 (days)	Mean	99.8	102.1	100.7
	Median	101.0	103.0	102.0
	SD	8.7	7.1	8.0
	MIN,MAX	84,112	89,111	84,112
	Q1,Q3	93,106	98,108	95,107
	n	17	11	28
	Nmiss	0	0	0
Calculated* Gestation - Visit 4 (days)	Mean	145.5	143.5	144.7
	Median	141.0	141.0	141.0
	SD	29.5	9.6	23.5
	MIN,MAX	125,252	126,166	125,252
	Q1,Q3	127,146	140,148	136,146
	n	17	11	28
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

Section 7. Myometrial biopsies - Glycogen storage

7.2.4.3 Gestation by timepoint - Visit 5 (28 Weeks), Visit 6 (36 Weeks)

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 5 (days)	Mean	195.8	193.7	195.0
	Median	195.5	196.0	196.0
	SD	5.4	9.6	7.2
	MIN,MAX	182,207	167,201	167,207
	Q1,Q3	194,199	196,197	194,198
	n	16	10	26
	Nmiss	1	1	2
Calculated* Gestation - Visit 6 (days)	Mean	255.3	252.3	254.2
	Median	255.5	252.0	253.5
	SD	3.8	4.6	4.3
	MIN,MAX	248,263	245,260	245,263
	Q1,Q3	253,258	251,256	252,258
	n	16	10	26
	Nmiss	1	1	2

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations

*These calculations rely on the accuracy of the recorded date of visit

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DOI: 10.3310/eme03070

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Section 7. Myometrial biopsies - Glycogen storage

7.2.4.4 Gestation by timepoint - Visit 7 Term, Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Calculated* Gestation - Visit 7 (days)	Mean	276.4	273.6	275.5
	Median	275.0	273.0	274.0
	SD	5.4	1.5	4.6
	MIN,MAX	271,289	272,276	271,289
	Q1,Q3	273,277	273,274	273,276
	n	10	5	15
	Nmiss	7	6	13
Calculated* Gestation - Visit 8 (days)	Mean	276.0	276.1	276.0
	Median	275.0	274.0	274.5
	SD	8.8	10.8	9.4
	MIN,MAX	257,292	263,306	257,306
	Q1,Q3	273,280	271,278	273,280
	n	17	11	28
	Nmiss	0	0	0

N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*These calculations rely on the accuracy of the recorded date of visit

Section 7. Myometrial biopsies - Glycogen storage

7.2.4.5 Gestation by timepoint - Visit 8 Delivery

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		---------Allocated_Intervention---------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Recorded* Gestation - Visit 8 (days)	Mean	274.9	272.5	273.9
	Median	274.0	273.0	273.0
	SD	7.7	4.2	6.6
	MIN,MAX	256,290	263,280	256,290
	Q1,Q3	273,280	270,274	272,277
	n	17	11	28
	Nmiss	0	0	0
Coded R_gestation - Visit 8 (n(%))	>24 and <=37 WEEKS	1 (5.9)	0	1 (3.6)
	>37 WEEKS	16 (94.1)	11 (100)	27 (96.4)

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N = number of patients randomised, n = the number of observations, Nmiss = number of missing observations
*Actual recorded value

By: Aryelly Rodriguez - ECTU Statistician

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Section 7. Myometrial biopsies - Glycogen storage

7.2.5 Delivery Details - alive births

Population = Intention to treat (ITT) - AllocatedTreatment used for summarisation

		--------Allocated_Intervention--------		
Parameter(s)	*Categories*	*Placebo*	*Metformin*	*Overall*
Delivery Method (n(%))	LSCS in labour	4 (23.5)	1 (9.1)	5 (17.9)
	LSCS pre labour	13 (76.5)	10 (90.9)	23 (82.1)
C-SECTION index pregnancy (n(%))	Yes	17 (100)	11 (100)	28 (100)
Primary C-SECTION in index pregancy (n(%))	Yes	8 (47.1)	4 (36.4)	12 (42.9)
	No	9 (52.9)	7 (63.6)	16 (57.1)

Appendix 7 Placental biopsy sample collection

EMPOWAR Placenta sampling collection
Working Practice Document (WPD)

EMPOWAR WPD number:	9
Version:	Draft
Author:	Fiona Denison

Authorised by: _____

Prof. Jane E. Norman

_____

Date authorised:

Effective Date:

1. PURPOSE

The purpose of this WPD is to describe the process for collecting and preparing the placenta samples for adult participants in the EMPOWaR study and to ensure that all participating sites are consistent in their methods of collection and storage. This document should be retained in the ISF, section 7.

2. DEFINITIONS

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ISF Investigator Site File
PI Principle investigator at the site
WPD Working Practice Documents

3. WHY

The specific guidelines for taking placenta samples are created to help ensure accuracy and repeatability across the participating sites

4. WHO

This WPD applies to all staff delegated by the PI for the task of collecting and preparing samples.

5. PROCEDURE

Two methods of placental collection are described.

All sites should use the STANDARD COLLECTION PROTOCOL.

The **ENHANCED COLLECTION PROTOCOL** should only be used by sites that have the research infrastructure available to support the more in-depth sample processing.

5.1 Standard collection protocol (ALL SITES)

5.11 RNA samples

- Cut a piece of placenta (no covering membranes) about 10mm x 10mm x 10mm and divide into four pieces.
- Place the pieces into a pot containing RNAlater.
- Transfer to research laboratory
- After a 24hrs, remove RNAlater solution and store samples in labelled microtube (1 sample per tube) at -80C until subsequent analysis and/or transfer to Edinburgh.

5.2 Enhanced collection protocol / sample processing (ONLY in sites able to accommodate extended sample processing required)

5.21 RNA samples

- Cut a piece of placenta (no covering membranes) about 10mm x 10mm x 10mm and divide into four pieces.
- Place the pieces into a pot containing RNAlater.
- Transfer to research laboratory
- After a 24hrs, remove RNAlater solution and store samples in labelled microtube (1 sample per tube) at -80C until subsequent analysis and/or transfer to Edinburgh.

5.22 Frozen samples:

- With placenta membrane side down, cut a piece of placenta of 1cm x 1cm x 1cm from a cotyledon at the centre of the placenta and cut into four pieces.
- Place the pieces into a small 'frozen' tube
- Snap-freeze samples at -80C
- Deliver samples to research laboratories and store at -80C until subsequent analysis and/or transfer to Edinburgh.

5.23 Histology samples

- With placenta membrane side up, cut a piece from the centre of a cotelydon full thickness from the maternal to fetal side, at least 10mm wide.
- Place this into a universal container containing 10% neutral buffered formalin (NBF)
- Deliver samples to research laboratory
- Fix samples in NBF for 24hrs
- Remove formalin and cover sample with 70% IMS
- Store in 5C fridge until subsequent processing and/or transfer to Edinburgh.

6. TRANSFER OF FROZEN SAMPLES (or other samples)

Transfer of frozen samples to the University of Edinburgh.

The research team at the University of Edinburgh should be contacted to arrange receipt of the samples before any arrangements are made for transfer (see contact details below).

Human clinical or research specimens may contain infectious biological agents which are hazardous to health. The transport regulations within the UK are based upon the UN Model Regulations for the Transport of Dangerous Goods. The latest revision of

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this set of regulations was prepared by the Department for Transport (DfT) authority (Revision 5: February 2011).
Blood samples taken as part of the EMPOWAR clinical trial will be in UN Model Regulations category B and must be consigned/shipped frozen in dry ice as UN3373 using a locally approved courier. The courier should provide specific information on their approved **labelling** and shipping **documentation** which must comply with the P650 packing instruction required by the UN 3373 code. Full details of the code can be obtained at:-
http://www.dft.gov.uk/426155/425453/800_300/infectioussubstances.pdf

Samples sent should be transferred with a copy of the EMPOWaR tissue collection log.

Contact details to arrange the collections:

Sonia Whyte
EMPOWaR Trial Manager
xxxxx

Appendix 8 Myometrial biopsy collection

Procedure for the collection and handling of myometrial biopsies prior to the measurement of uterine contractility at the University of Liverpool

For centres (Liverpool Womens, Arrowe park and Whiston hospitals) that will be collecting myometrial biopsies for *in-vitro* measurement of uterine contractility as well as measurement of glycogen.

This document should be read in association with EMPOWaR WPD6 the collection and handling of myometrial biopsies, Version 1.0.

Elective Caesarean Sections

Please contact members of the research team at the University of Liverpool as soon as a date for the CS has been arranged.

Surgeons

Excise a **1 - 2cm^3** of myometrium and cut into two pieces (**biopsy A** and **Biopsy B**; each around 1cm^3 of myometrium) from the uterine incision (**muscle only, not full thickness**).

Surgeon/scrub nurse

Biopsy A (fresh biopsy)

Place into Hanks Balanced Salt Solution (pink HBSS; this will be provided by the University of Liverpool) and place in the fridge until collection by a member of the University of Liverpool research team.
*****NB, DO NOT FREEZE THIS PORTION OF THE BIOPSY*****

Biopsy B (frozen biopsy; see EMPOWaR WPD6 The collection and handling of myometrial biopsies, Version 1.0.

In brief

Immediately (i.e. within 30 seconds), drop the **biopsy B** into:-

a) Liquid nitrogen or isopentane cooled in dry ice (flash freezing)

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or, if this is not available in theatre,

b) 100ml Modified Hanks' Balanced Salt Solution (clear) or physiological saline previously **cooled to 4^0C**. This biopsy should then be frozen (dry not in solution) ASAP and stored as detailed in EMPOWaR WPD6

Emergency Caesarean Sections

- If possible (e.g. during the day) proceed as for Elective CS
- During out of hours cover it is unlikely that myometrial samples will be frozen within a few minutes of collection. The following protocol is therefore designed to maximise availability of **fresh** samples for the contractility experiments. Please contact members of the research team at the University of Liverpool as soon as it is know that a caesarean will be performed.

Surgeons

Excise a single biopsy of **1 - 2cm^3** of myometrium) from the uterine incision (**muscle only, not full thickness**).

Surgeon/scrub nurse

Place biopsy into Hanks Balanced Salt Solution (This HBSS is pink and will be provided by the University of Liverpool) and store in the fridge until collection by a member of the University of Liverpool research team,

LABELLING

The sample container should be clearly labelled with:

Date and time of collection

EMPOWAR study ID

BIOPSY STORAGE

Biopsy samples for the contractility experiments at the University of Liverpool can be stored in the **Hanks' Balanced Salt Solution** at the local site at 4°C . If it has not been possible for a member of the University of Liverpool research team to collect the sample within 36 hours of the surgery then the sample should be disposed of in accordance with local procedures for disposal of human clinical waste.

EQUIPMENT

- **Hanks' Balanced Salt Solution (pink) for biopsy samples for contractility experiments.** This can be purchased Sigma Aldrich, catalogue number H9269 or will be provided by the University of Liverpool Research Team.

- **Sample containers,** for fresh biopsies. A wide variety of 20 – 50ml universal containers would be suitable e.g. Sigma catalogue no Z645362

Contact details for the University of Liverpool Research Team

xxxxxxxx

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Appendix 9 Public and patient involvement

Recruitment of study participants was challenging. The majority of women approached declined to participate. Anecdotally, this was predominantly because of a concern about taking medication during pregnancy. However, it was also evident that there was a lack of awareness of the problems associated with obesity during pregnancy, particularly potential longer-term harms for the offspring. We held education sessions for study midwives to enable them to pass on this message to their patients and the wider midwifery community. We distributed posters advertising the study to all clinical areas where potentially eligible women might see them. Following feedback from the public and potential patients that they found the word 'obese' offensive, we revised all of our materials and used the more acceptable terminology 'high BMI'. We employed the use of social media and a website to disseminate information to the public and participants about the progress of the trial, for example updates when recruitment targets had been reached. We included a qualitative substudy to explore the reasons behind patients' reluctance to participate in the trial and why participants withdrew from the trial once they had been recruited.

Patients and the public were not formally involved in the trial at the design and concept stage. However, the clinical investigators (including the lead investigator) were strongly influenced by the pregnant women (patients) they look after and these influences were key to the trial.

Patient/public involvement was formally instituted during the conduct of the trial. A patient/public representative was appointed to the Trial Steering Committee. She made helpful comments on the patient information leaflet and attended several meetings of the Trial Steering Committee. She resigned in the last year of the study and, given that the trial was ending, she was not formally replaced.

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