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

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Scientific summary

Reducing birthweight in babies of obese pregnant women

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.

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 $\geq$ 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 $\geq$ 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 $\geq$ 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.

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 ≥ 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.

Trial registration

This trial is registered as ISRCTN51279843.

Funding

Efficacy and Mechanism Evaluation

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