

Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee

N Waugh, P Royle, C Clar, R Henderson,
E Cummins, D Hadden, R Lindsay
and D Pearson



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Abstract

Screening for hyperglycaemia in pregnancy: a rapid update for the National Screening Committee

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Background: Screening for gestational diabetes has long been a controversial topic. A previous Health Technology Assessment (HTA) report reviewed literature on screening for gestational diabetes mellitus (GDM) and assessed the case for screening against the criteria set by the National Screening Committee.

Objective: To update a previous HTA report which reviewed the literature on screening for GDM by examining evidence that has emerged since that last report, including the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), the Maternal and Fetal Medicine Units Network (MFMUN) trial and the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. To review data on recent trends in maternal age at birth and on the prevalence of overweight and obesity and the effect on prevalence of GDM.

Data sources: A systematic review and meta-analysis of the literature was carried out. The bibliographic databases used were MEDLINE (1996 to January 2009), EMBASE (1996 to December 2009), the Cochrane Library 2008 issue 4, the Centre for Reviews and Dissemination database and the Web of Science.

Review methods: For the review of treatment with oral drugs versus insulin, a full systematic review and meta-analysis was carried out. The results of the ACHOIS, MFMUN and HAPO studies were summarised and their implications discussed. Findings of a selection of other recent studies, relevant to the continuum issue, were summarised. Some recent screening studies were reviewed, including a particular focus on studies of screening earlier in pregnancy.

Results: The HAPO results showed a linear relationship between plasma glucose and adverse outcomes – there is a continuum of risk with no clear threshold which could divide women into those with gestational diabetes and those without. There

was good evidence from trials and the meta-analysis that women who fail to control hyperglycaemic in pregnancy on lifestyle measures alone can be safely and effectively be treated with oral agents, metformin or glibenclamide, rather than going directly to insulin. Evidence showed few differences in results between glibenclamide and insulin and metformin and insulin. The exceptions were that there was less maternal hypoglycaemia with glibenclamide, but less neonatal hypoglycaemia and lower birthweight with insulin, and there was less maternal weight gain with metformin. The ACHOIS and MFMUN trials showed reductions in perinatal complications among infants born to mothers who were provided with more intensive dietary advice, blood glucose monitoring and insulin when required. The HAPO study demonstrated adverse outcomes over a much wider range of blood glucose (BG) than the traditional definition of GDM. In the HAPO study, no one measure of BG came out as being clearly the best, although fasting plasma glucose (FPG) was as good as any, and had advantages of being more convenient than an oral glucose tolerance test (OGTT), but correlations between fasting and post-load levels were quite poor. Two screening strategies dominated; (1) selection by the American Diabetes Association criteria followed by the 75-g OGTT [incremental cost-effectiveness ratio (ICER) £3678], and (2) selection by high-risk ethnicity followed by the 75-g OGTT (ICER £21,739). Studies indicated that costs are about £1833 higher for pregnancies complicated by gestational diabetes, suggesting that prevention would be worthwhile.

Limitations: Not all of the HAPO results have been published, and none of the reviewed economic studies resolved the most difficult issue – at what level of BG does intervention become cost-effective?

Conclusions: The evidence base has improved since

the last HTA review in 2002. There is now good evidence for treatment of oral drugs instead of insulin and it looks increasingly as if FPG could be the test of choice. However some key uncertainties remain to be resolved, which can be done by further analysis

of the already collected HAPO data and by using the UK model used in developing the NICE guidelines to assess the cost-effectiveness of intervention in each of the seven HAPO categories.



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List of abbreviations

| | | | |
|-------------------|---|-------|--|
| A | acarbose | IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| ACHOIS | Australian Carbohydrate Intolerance Study in Pregnant Women | LGA | large for gestational age |
| ADA | American Diabetes Association | M | metformin |
| BG | blood glucose | N/A | not applicable |
| BMI | body mass index | N/R | not reported |
| CG | capillary glucose | NICE | National Institute for Health and Clinical Excellence |
| CI | confidence interval | NICU | neonatal intensive care unit |
| FBG | fasting blood glucose | NSC | National Screening Committee |
| FCG | fasting capillary glucose | OGCT | oral glucose challenge test |
| FPG | fasting plasma glucose | OGTT | oral glucose tolerance test |
| G | glibenclamide | OR | odds ratio |
| GCT | glucose challenge test | PG | plasma glucose |
| GDM | gestational diabetes mellitus | PPG | post-prandial glucose |
| HAPO | Hyperglycemia and Adverse Pregnancy Outcomes Study | QALY | quality-adjusted life-year |
| HbA _{1c} | glycated haemoglobin | RCT | randomised controlled trial |
| HGP | hyperglycaemia in pregnancy | RR | relative risk |
| HTA | Health Technology Assessment | SD | standard deviation |
| I | insulin | SGA | small for gestational age |
| IGT | impaired glucose tolerance | SIGN | Scottish Intercollegiate Guidelines Network |

| | | | |
|------|---------------------------|-----|--------------------------|
| T2DM | type 2 diabetes mellitus | WMD | weighted mean difference |
| WHO | World Health Organization | | |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

Hormonal changes in pregnancy make the body less sensitive to naturally produced insulin. In some women, this can lead to blood glucose (BG) levels being higher than normal. As a result, the baby's BG is higher than normal, and it responds by increasing its own insulin production. This can lead to a number of problems. The baby's higher than normal insulin can lead to overgrowth of fatty tissues, and it may be larger than usual. This can lead to problems at delivery, with shoulders being a particular problem, with occasional fractures of arms and damage to the nerves to the arm. Delivery has to be by caesarean section more often. After birth, the baby's BG may fall too low (neonatal hypoglycaemia) because its own insulin is inappropriately high. Babies are more prone to respiratory problems, and often have to be admitted to neonatal intensive care. Death (perinatal mortality), while rare, is more common than in babies of women who do not have gestational diabetes.

Screening for gestational diabetes has long been a controversial topic. Even the definition of what is gestational diabetes varies. This report is concerned mainly with disorders of glucose regulation which come on in pregnancy and remit afterwards. Some women found to have raised glucose levels in pregnancy will have previously undiagnosed type 2 diabetes mellitus (T2DM).

A previous Health Technology Assessment report reviewed the literature on screening for gestational diabetes mellitus (GDM), published up to the middle of 2000. The main findings were that:

- There were many different definitions.
- The WHO (World Health Organization) criteria for gestational diabetes include a much wider range of hyperglycaemia than in non-gestational diabetes, including impaired glucose tolerance (IGT) as well as diabetes.
- There was almost certainly a continuum of risk, rather than there being two distinct groups of normal and abnormal.

- The key risk factor might be maternal overweight leading to glucose intolerance.
- Diseases should be defined by the harm they do. The early definitions of GDM were based on levels which predicted later diabetes in the mother. Later ones incorporated fetal risk. However that was often based on 'macrosomia' which was arbitrarily based on birthweight of 4000 g (about 8 lbs 11 oz) or 4500 g. Basing it on weight does not distinguish between large healthy babies, and those with the unhealthy insulin-driven overgrowth of adipose tissue.
- There was a need to define GDM more precisely, based not on arbitrary cut-offs of BG, but on the level at which outcomes of pregnancy worsened significantly. Outcomes include neonatal health, caesarean section rates, and maternal anxiety, inconvenience and other disbenefits.
- Universal screening did not appear justified, so the approach might be to screen women with factors known to increase the risk, such as age, ethnicity and obesity.
- Another problem was which measure of BG to use. The leading competitors included fasting plasma glucose (FPG) and the 50-g challenge test.
- The optimum thresholds for positive screening tests were uncertain.
- Treatment options included diet and exercise, and insulin. However it was noted that trials of oral agents such as metformin were under way.
- Screening for GDM failed to meet some of the National Screening Committee (NSC) criteria.

The report noted that a number of relevant studies were under way. These included:

- The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), which was investigating the effect of screening for, and management of, glucose intolerance in pregnancy in approximately 1000 women.
- The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study, which was examining the links between the level of BG, and the risk of adverse maternal, fetal and neonatal outcomes, in approximately 25,000 women

from the USA, Canada, Europe (including Belfast), Asia and Australia.

What has changed?

The ACHOIS and HAPO studies have now been published, though not all the results of HAPO have yet appeared.

Data on recent trends in maternal age at birth, and on the prevalence of overweight and obesity, indicate that women are older and heavier when having children, which will increase the prevalence of gestational diabetes.

The key questions for this updating review

1. After HAPO and similar studies, at what level of hyperglycaemia in pregnancy (HGP) should we intervene? At the high end of plasma glucose (PG), there will be definite benefits to the baby and the benefits will outweigh the harms and inconveniences. But at the lower end of the hyperglycaemia distribution (which could be just above the upper limit of normal) the harms and inconveniences may outweigh the benefits.
2. Which BG screening test should be used?
3. Should there be universal PG testing, or selection by risk factors so that only a proportion of women proceed to blood testing?
4. Are oral glucose lowering drugs effective and safe? Should the treatment pathway be lifestyle, then oral agents, then insulin?
5. What are the research needs now?

Methods

For the review of treatment with oral drugs versus insulin, a full systematic review and meta-analysis was carried out.

The results of ACHOIS and HAPO were summarised and their implications discussed. Findings of a selection of other recent studies, relevant to the continuum issue, were summarised.

Some recent screening studies were reviewed, including a particular focus on studies of screening earlier in pregnancy.

Results

The HAPO study showed that there was a continuum of risk with no threshold which could divide women into those with gestational diabetes, and those without. There was a linear relationship between plasma glucose (PG) and adverse outcomes. This makes it inappropriate to classify some women as having gestational diabetes, and the rest not. It is probably better to avoid the dichotomous term gestational diabetes and to talk instead of 'hyperglycaemia in pregnancy' (HGP). In the HAPO study, from results published so far, macrosomia has been defined by birthweight, but head circumference data were also collected.

Other studies published in recent years provided further evidence for the continuum.

Treatment with oral drugs instead of insulin

We identified a total of 27 primary studies, including some published only as conference abstracts. Four randomised controlled trials (RCTs) and 11 observational studies compared glibenclamide with insulin. One RCT also included a group receiving acarbose. Three RCTs and three observational studies compared metformin with insulin.

The RCT evidence showed few differences in results between glibenclamide and insulin. There were no differences in most outcomes. There was less maternal hypoglycaemia with glibenclamide, but less neonatal hypoglycaemia and lower birthweight with insulin.

There were also no differences in most outcomes when comparing metformin with insulin. There was less maternal weight gain with metformin.

Both glibenclamide and metformin are safe and effective, and can be used instead of, or before insulin when diet and physical activity fail. Neither drug has yet been licensed for use during pregnancy. Not surprisingly, there is evidence that women prefer oral agents.

Some factors predicted failure to achieve adequate glycaemic control on oral agents, but the current evidence base is not sufficient to rule out a trial of oral treatment after failure of diet alone. If adequate control is not quickly obtained, a switch could be made to insulin. However, it appears that insulin therapy is not a guarantee of achieving

adequate glycaemic control. In studies measuring glucose levels among women receiving insulin, a significant proportion was found to have suboptimal glycaemic control.

One trial compared glibenclamide and metformin and found that failure to achieve glycaemic control was more common among women receiving metformin (41% vs 20%).

However, it appears that insulin therapy is not a guarantee of achieving adequate glycaemic control. In studies measuring glucose levels among women receiving insulin, a significant proportion was found to have suboptimal glycaemic control.

Thresholds for intervention

The continuum of risk by glucose level shown by HAPO creates a problem in that there is no clear clinical threshold for intervention. Most of the adverse outcomes occur in low risk groups – about half in HAPO categories 2 and 3 – because those groups are much larger. However the numbers needed to treat to avoid an adverse outcome in those groups are much larger (33 and 25, respectively) than in categories 6 and 7 (9 and 6, respectively). However only 12% of the adverse outcomes occur in categories 6 and 7, because the numbers of women in these groups are much smaller.

Screening studies

Early screening

Studies reporting that screening at first antenatal clinic was worthwhile did not all distinguish between early onset of gestational hyperglycaemia and pre-existing T2DM. The rising prevalence of T2DM at younger ages, linked with overweight and obesity, and the older ages of women having pregnancies means that increasing numbers will be diagnosed with T2DM in pregnancy. Glycated haemoglobin may be useful for detecting pre-gestational diabetes, and does not require fasting or glucose loading.

There might be a case for pre-conceptual testing in high risk groups.

Choice of test

In the HAPO study, no one measure of BG came out as being clearly the best, but FPG was as good as any, and has the advantages of being more convenient than the oral glucose tolerance test (OGTT). It might be easier done in general

practice in view of the practical difficulties of doing a large number of fasting glucose tests in hospital antenatal clinics. Adherence to fasting might not be universal. However, correlations between the fasting and post-load levels were quite poor, and we need to know how many of the women in the low risk HAPO categories were high risk by post-load levels.

Selective or universal screening

The National Institute for Health and Clinical Excellence (NICE) recommends selective screening based on body mass index (BMI) over 30 kg/m², previous GDM, previous baby over 4500 g, a family history of diabetes, or on high risk ethnicity. This recommendation was based on the probability of being diagnosed with GDM on the basis of the 75-g OGTT, and pre-dates HAPO. It would be useful to have data on the prevalence of risk factors in each of the seven HAPO categories, to see if selective screening would miss many women in the higher risk categories.

Economic studies

Most studies of costs or cost-effectiveness pre-dated HAPO. In brief:

- Costs are about £1833 higher for pregnancies complicated by gestational diabetes, suggesting that prevention would be worthwhile.
- Costs are lower for treatment with oral agents than with insulin.
- The economic analysis of the ACHOIS study found that intervention with more intensive dietary advice, blood monitoring and insulin when required, resulted in a cost per serious perinatal event avoided of £12,688. The (statistically not significant) impact upon perinatal mortality suggested a cost per life-year of £1376.
- Some studies find that screening with the 50-g glucose challenge test and then testing screen-positives with the OGTT, was less costly than going straight to universal OGTT.

A high quality cost-effectiveness analysis was provided for the NICE Guideline Development Group. Full details are available on the NICE website. It found that two screening strategies dominated:

- selection by the American Diabetes Association (ADA) criteria followed by the 75-g OGTT [incremental cost-effectiveness ratio (ICER) £3678]

- selection by high-risk ethnicity followed by the 75-g OGTT (ICER £21,739).

However, the economics studies do not yet resolve the most difficult issue – at what level of BG does intervention become cost-effective? One study addresses that issue, but is only available as an abstract. It uses US costs, and concludes that lowering the threshold for intervention from HAPO category 5 to category 4, based on the 2-hour glucose results, would not be cost-effective. No similar analysis has yet been done for the UK.

Revisiting the National Screening Committee criteria

Some of the criteria that were not met in the last HTA review have now been met:

- Criterion 1: importance of problem. Met. The condition has become more important, because of rising prevalence, and the HAPO demonstration of adverse outcomes over a much wider range of BG.
- Criterion 3: primary prevention. Debatable. Public health campaigns have not prevented the rise in general population obesity, but primary prevention has not been tried specifically in women planning pregnancy.
- Criterion 5: cut-off level defined. Not yet met, pending further cost-effectiveness analysis post-HAPO.
- Criterion 7: Partially met. HAPO has shown that a single measure of BG is highly predictive.
- Criteria 8 and 9: treatment. Met. The ACHOIS trial has shown that intervention at lower levels is cost-effective. Trials of oral drugs have shown they are safe and effective, as well as being cheaper and preferred by patients.
- Criterion 11: not met – still no RCTs of screening versus no screening.
- Criterion 13: overall benefits and harms. Partially met. The balance has swung towards easier testing and easier treatment, coupled with increasing prevalence.
- Criterion 14: met for some groups following the economic analyses by the ACHOIS group and for the NICE Guideline Development Groups, but still some uncertainties to be resolved.

Research needs

1. Could we use FPG for screening? We need further analysis of the HAPO data to determine how many women in categories 1–4 by FPG are in categories 5–7 by post-load PG.
2. What are the true rates of macrosomia within the HAPO categories, as assessed by both birthweight and head circumference?
3. Is glycated haemoglobin (HbA_{1c}) a useful test at booking clinic for detecting pre-gestational diabetes, and also pre-gestational insulin resistance likely to be followed by HGP?
4. Can risk factors, in conjunction with HbA_{1c}, identify a group of women whose risk of adverse outcomes is very low and who need not be screened? HAPO data could be used to address the question of selective or universal screening, by comparing risk factors and different thresholds in each category. The hypothesis might be that women with risk factors are more likely to be in the higher categories.
5. What is the most cost-effective screening and treatment strategy, in the light of the new evidence? At which HAPO category does treatment become cost-effective, taking into account infant and maternal outcomes, and treatment with the cheaper oral agents when lifestyle measures fail, with insulin being used only when the oral drugs fail? Resources in this mini-review did not permit new modelling. We recommend that the team which did the modelling for the NICE Guideline Development Group should be asked to update their analysis. One of the issues in modelling is the relative weight given to each of the adverse outcomes.
6. Could public health interventions reduce the prevalence of obesity among women becoming pregnant in the UK, and therefore reduce the problem at source?
7. Given the increasing age and weight of mothers-to-be, should screening start earlier? Screening is usually done at 24–28 weeks. Several commentators have noted that there can be delays between screening, diagnostic testing and treatment, and that these can occur during the ‘therapeutic window’ and hence result in poorer outcomes. There is a need for studies which report the prevalence of HGP by week of gestation, perhaps at 2-week intervals. Such studies could identify the optimum time to screen, perhaps depending on age and BMI.

Conclusions and recommendation

Despite advances in knowledge following the ACHOIS and HAPO studies, some key uncertainties remain to be resolved. Some of these could be resolved by, firstly, further analysis of the already collected HAPO data, and, secondly, by updated modelling using the UK model used in developing the NICE guidelines, and for each of the seven HAPO categories.

We recommend that the NSC should ask for, and await, additional analyses before revising its policy.

It would be wrong to make firm recommendations now given the knowledge gaps and the fact that data will be available from the HAPO study which can fill some of the gaps. The uncertainty about the level at which intervention is justified may come out of the recommended modelling.

There is also a need for interventions aimed at prevention of HGP, firstly by persuading women to achieve normal weight before becoming pregnant, and secondly by physical activity and appropriate diets in pregnancy.

Chapter I

Introduction

The previous Health Technology Assessment review

Screening for gestational diabetes has long been a controversial topic. Even the definition of what is included varies. Strictly speaking gestational diabetes should refer to diabetes which comes on during pregnancy and resolves after delivery, but both the Scottish Intercollegiate Guidelines Network (SIGN) Guideline No. 116¹ and the National Institute for Health and Clinical Excellence (NICE) guideline on diabetes in pregnancy² have used the World Health Organization (WHO) description of diabetes with first onset in pregnancy. In the USA the definition does not require post-natal resolution, so the US label of gestational diabetes mellitus (GDM) can include true type 2 diabetes mellitus (T2DM) with onset, or just diagnosis, during pregnancy.

A previous Health Technology Assessment (HTA) report³ reviewed the literature on screening for GDM, published up to the middle of 2000. It also assessed the case for screening against the criteria of the National Screening Committee (NSC) (available on NSC website⁴). The main findings were that:

- There was still debate about what was meant by GDM. The threshold for diagnosis was not clear, and what was called GDM usually included impaired glucose tolerance. There were many different definitions, perhaps reflecting the history of GDM, which was originally defined on the basis of the mother's risk of later development of T2DM. In recent years the focus has been more on harms to the baby.
- The criteria for gestational diabetes, as defined by the WHO in 1998,⁵ used a cut-off of 7.0 mmol/l for fasting and of 7.8 mmol/l for the 2-hour post oral glucose tolerance test (OGTT) levels, which meant that a much larger range of hyperglycaemia was included than in non-gestational diabetes, including impaired glucose tolerance (IGT) as well as diabetes. Various studies showed that what was classed

as GDM using non-pregnant diagnostic levels was in fact mainly IGT. This failed to take into account the physiological rise in post-prandial glucose (PPG) levels in pregnancy. In a Swedish study,⁶ the mean 2-hour plasma glucose (PG) level was 8.0 mmol/l; if the WHO criteria were applied, 18% would have had GDM.

- There was almost certainly a continuum of risk, rather than there being two distinct groups of normal and abnormal.
- The key risk factor might be maternal overweight leading to glucose intolerance.
- Diseases should be defined by the harm they do. The early definitions of GDM were based on levels which predicted later diabetes in the mother. Later ones incorporated fetal risk. However, that was often based on 'macrosomia', which was arbitrarily based on a birthweight of 4000 g (about 8 lbs 11 oz) or 4500 g. Basing it on weight does not distinguish between large healthy babies, and those with the unhealthy insulin-driven overgrowth of adipose tissue. And cut-offs of 4000 and 4500 are chosen for neatness, and are not based on physiology or pathology.
- One issue was whether to have universal screening, or selected screening based on risk factors. A policy of universal screening did not appear justified, so the approach might be to screen women with factors known to increase the risk, such as age, ethnicity and obesity. However, risk factors have low sensitivity and specificity.
- Another problem was which measure of blood glucose (BG) to use. The leading competitors amongst possible tests included fasting plasma glucose (FPG) and the 50-g glucose challenge test (GCT). However the former would miss post-prandial hyperglycaemia, which as Fraser (1995)⁷ and Jovanovic (2002)⁸ have argued, may be enough to cause overgrowth of some fetal tissues. The literature did not give a clear answer as to which of FPG or the 50-g challenge test was better. The cost per case found was similar.
- The optimum thresholds for positive screening tests were uncertain. The threshold for the FPG might have to be as low as 4.7 mmol/l

in order to provide sufficient sensitivity. The most commonly cited thresholds for the GCT were 7.2 mmol/l and 7.8 mmol/l. These seemed too low and the report favoured a cut-off of 8.2 mmol/l for the GCT.

- Treatment options included diet and exercise, and insulin. However it was noted that trials of oral agents such as metformin were under way.
- Screening for GDM failed to meet some of the NSC criteria.

The case for screening was assessed against the NSC criteria as follows. The full details are given in the previous HTA report.³ (Note that the criteria numbers are as used in 2001 and are different from those in the current list, which has been expanded to cover genetic screening.)

(1) The condition should be an important health problem

When considering whether this criterion was met, the last report gave it a verdict of borderline, on the grounds that a low proportion of births were adversely affected, though noting that the consequences were serious for some individuals.

The main harm is to the infant. When maternal BG is high, glucose crosses the placenta into the baby's blood, causing it to produce more insulin than usual. This causes a number of problems. The first is macrosomia, whereby the baby has increased growth but with an unhealthy pattern, with overgrowth of insulin-sensitive tissues such as adipose tissue, especially around chest, shoulders and abdomen. This can cause difficulties during birth, known as 'shoulder dystocia' – a lay translation might be 'getting stuck on the way out'.

Another form of harm is neonatal hypoglycaemia – the baby's blood sugar falls after birth, because it is then deprived of the maternal glucose supply but is still overproducing its own insulin.

There are also harms to the mother, and these come partly from the diagnosis rather than the condition. Mothers with GDM are much more likely to have to deliver by caesarean section, and this often happens when the baby's weight is normal – the diagnosis alone may increase the rate of delivery by section.⁹ There may be adverse effects of treatment, which has until recently been first with diet and then with insulin. Langer *et al.* (1989)¹⁰ noted that mothers with the tightest control of GDM had more small for gestational age (SGA) infants.

(2) The epidemiology and natural history of the condition, including development from latent to developed disease, should be adequately understood, and there should be a detectable risk factor, or disease marker, and a latent period or early asymptomatic stage

This criterion was considered to have been met.

(3) All the cost-effective primary prevention interventions should have been implemented as far as practicable

The previous report concluded that this criterion had not been met. It noted that most GDM was related to maternal overweight, and that primary prevention would include interventions to persuade women planning pregnancies to get down to normal weight and be physically active.

(4) There should be a simple, safe, precise and validated screening test

This was considered to have been partially met – there were simple and safe tests, but validation was lacking.

(5) The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

The problem here was that the distribution of test values was known, but that the cut-off level was uncertain. Should the usual WHO thresholds be used, or should higher cut-offs be used to reflect the normal elevation of BG in pregnancy?

Agarwal and Dhatt (2007)¹¹ noted the continuing confusion and provided a table illustrating the range of levels considered diagnostic in the criteria of different organisations. For FPG the level ranged from 5.3 mmol/l (Canadian Diabetes Association, American Diabetes Association – ADA) to 7.8 mmol/l (WHO 1985, cited in Agarwall and Dhatt 2007¹¹), with various intermediate levels such as 5.8 mmol/l (National Diabetes Data Group, USA – NDDG) and 6.0 mmol/l (European Association for the Study of Diabetes – EASD). The level considered diagnostic at 2 hours ranged from 7.8 mmol/l (WHO 1999, cited in Agarwall and Dhatt 2007¹¹) to 9.2 mmol/l (NDDG) with a wide spread in between, including 8.0 mmol/l (Australia), 8.3 mmol/l (Japan Diabetes Society), 8.6 mmol/l (ADA and France), 8.9 mmol/l (Canada) and 9.0 mmol/l (EASD).

(6) The test should be acceptable to the population

Met.

(7) There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

This criterion was not met because of the lack of consensus in international evidence and guidelines on what test to use as the definitive diagnosis. In the UK, standard practice appeared to be to use the 75-g OGTT, an unphysiological test with poor reproducibility. In other countries, the OGTT was done with a glucose load of 100 g (USA) or 50 g (Australia). One study¹² noted that using WHO criteria rather than US ones would reduce the number diagnosed as having GDM by about half.

(8) There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

The previous HTA report took a fairly hard line on this and concluded that it was uncertain whether this was met, because treatment trials reported mainly the incidence of macrosomia (based on weight alone) rather than adverse outcomes such as birth trauma or caesarean section.

(9) There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

This was only partially met. There was agreement about treating women with the highest glucose levels, but uncertainty, as illustrated by disagreement amongst guidelines and policies, about management of lesser degrees of hyperglycaemia.

(10) Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme

The last HTA report concluded that this had been met, because the treatments – diet, insulin and BG monitoring – were all standard ones. In retrospect, the bit about ‘all health care providers’ might have been considered more, perhaps by reviewing results from audits.

(11) There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity

No randomised controlled trials (RCTs) of screening (and intervention) versus no screening had been done. There had been a natural experiment in Ontario, where screening had been implemented in most areas, the exception being in the Hamilton area (the location of the evidence-based centre in McMaster). Wen *et al.* (2000)¹³ reported that there had been a steep rise in the prevalence of reported GDM in the rest of Ontario, but not in Hamilton. However, the proportions reported to have macrosomia (based on birthweight alone) were similar at 12.7% and 12.5%.

(12) There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public

The last assessment considered this had probably been met.

(13) The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

The harms of screening include the inconvenience of screening and diagnostic follow-up, worst if that involves an OGTT, the anxiety raised by positive screening tests, and the aforementioned effect of the diagnosis itself on section rates. However, the increase in section rates as reported in Canada⁹ was not seen in New South Wales.¹⁴ The harms of intervention also need to be considered, including insulin treatment and hypoglycaemia.⁷

Santini and Ales (1990)¹⁵ calculated that to prevent one case of macrosomia, 3716 women would need to be screened, and 134 more women would have caesarean sections. Furthermore, only 20–30% of babies of women with GDM have macrosomia,¹⁶ and a Cochrane review¹⁷ found that reducing macrosomia did not necessarily reduce rates of caesarean section, forceps delivery or birth trauma.

Some of the controversy arises because of differing perspectives. Those whose perspective is patient care are more likely to advocate screening but may disagree about how best to do it. Those whose perspective is a public health one are more likely

to think of opportunity costs and cost-effectiveness, and advocate a more restrictive approach.

The balance of benefit and harm will improve if:

- GDM becomes more common
- screening is more selective
- treatment is easier and has fewer side effects.

(14) The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money)

The last report concluded that it was uncertain whether this criterion had been met. No studies appeared to have produced a cost per quality-adjusted life-year (QALY) of screening and intervention for the UK. There were studies of the efficiency of screening in terms of cost per case of GDM found, with two strategies dominating others. These were the GCT in over 25 year olds with risk factors, using a cut-off of 8.2 mmol/l, and the FPG for all women. These gave similar costs per case found of around £488. However the FPG strategy found over twice as many cases, but at double the cost.

The cost-effectiveness of the screening and intervention programme would improve if:

- GDM became more common
- intervention costs fell
- intervention became more effective
- screening costs fell.

Some other criteria were not then met, but those concerned the management of the screening programme, and would not be met until a decision had been taken to have one.

The previous HTA report³ concluded that the main research gaps were as follows:

- There was a need to define GDM more precisely, based not on arbitrary cut-offs of BG, but on the level at which outcomes of pregnancy worsened significantly. Outcomes would include neonatal health, caesarean section rates, and maternal anxiety, inconvenience and other disbenefits.
- It was likely from the evidence, then, that there might be a continuum of risk in terms of BG levels, rather than a neat threshold dividing

pregnant women into normal with no risk and hyperglycaemic at risk.

- Further research was needed into the treatment of women who were hyperglycaemic in pregnancy, including those who had normal fasting glucose but abnormal post-meal levels (IGT of pregnancy). This is particularly relevant given rising levels of obesity, and hence insulin resistance, in the population.

The report noted that a number of relevant studies were under way. These included:

- The Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) study,¹⁸ a multi-centre trial led from Australia but with some UK centres. This study was investigating the effect of screening for, and management of, glucose intolerance in pregnancy in approximately 1000 women.
- The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study,¹⁹ which was examining the links between the level of BG, and the risk of adverse maternal, fetal and neonatal outcomes, in approximately 25,000 women from the USA, Canada, Europe (including Belfast), Asia and Australia.

What has changed?

Firstly, ACHOIS has now reported,¹⁸ and has shown that treatment of glucose intolerance (i.e. not just GDM) improves outcomes. The Maternal-Fetal Medicine Units Network trial of treatment of 'mild' gestational diabetes has also now reported.²⁰ A number of trials of oral agents have been published. A few new trials on non-pharmacological treatment have been published. It is thus timely to review the full range of treatment options, and we do this in Chapter 2.

Secondly, the main results of HAPO have also been published,¹⁹ and other studies of screening and the relationship between glucose levels and outcomes have been published since the last review. There is now a need for an update of the previous review in order to inform deliberations at NSC. The HAPO study and other results are described below.

Thirdly, there have been marked trends in two of the risk factors for GDM, maternal age and weight.

Data from England and Wales,²¹ (Table 1) shows that from 1998 to 2008 the number of live births to mothers in the 35–39 age group increased by

47%, and in the 40-and-over age group by 95%. This is contrasted with much smaller increases in the younger age groups, i.e. the under 25 age group has increased by 12%, the 25–29 age group remained virtually unchanged and the 30–34 age group increased by 2%. Also, it can be seen that, as a percentage of the total births for each year, the proportion to women 35 years and over has increased from 14.5% in 1998 to 20.1% in 2008.

Also, Scottish data show that the proportion of pregnancies to mothers under 25 has dropped by about half, whereas the proportion to mothers aged 30–34 had trebled (from about 4.5% in the 1970s to about 16% in recent years.²² For every year after the age of 25, the relative risk (RR) of developing GDM rises by 4% [Solomon *et al.* reported by Yogev *et al.* (2009)²³].

Data on weight from the Health Survey for England²⁴ show that the proportion of women aged 25–34 years with a body mass index (BMI) over 30 has risen from 11% in 1993 to 19% in 2007. For women aged 35–44 years, the proportion rose from 17% in 1993 to 24% in 2007. Data for single years 1993–2007 show that the proportion overweight has been fairly static around 32%, but the proportion obese has risen from 16% to 24%. By 2003, 55% of women aged 34–44 and 47% aged 25–34 years were overweight or obese. This is reflected in maternal obesity.

The Middlesbrough study²⁵ showed that the percentage of mothers who were obese has risen steadily, from about 10% in 1990 to 16% in 2004.

Hence women are getting heavier, and having children later. Both these factors will increase the proportion with hyperglycaemia in pregnancy. A US study by Getahun *et al.* (2008)²⁶ showed that the prevalence of GDM increased from 1.9% in 1989–90 to 4.2% in 2003–4.

The term ‘gestational diabetes’ may have outlived its usefulness, which is why we have used the term ‘hyperglycaemia in pregnancy’ (HGP) for this review. GDM means different things to different people, and most of what was called GDM was really IGT in pregnancy. The HAPO study should help with a revision of definitions.

The underlying hypothesis in gestational diabetes was set out by Pedersen in 1954.²⁷ In brief, maternal hyperglycaemia leads to fetal hyperglycaemia (because glucose crosses the placenta into the baby’s bloodstream) which stimulates fetal insulin release and hyperinsulinaemia. This causes excessive growth of certain tissues before birth, and after birth the withdrawal of maternal glucose leaves the baby at risk of hypoglycaemia because of its own over-production of insulin.

TABLE 1 Total numbers and percentages of live births for each maternal age group: 1998–2008

| Year | Under 25 | | 25–29 | | 30–34 | | 35–39 | | 40 and over | | Total births all ages |
|------------------------|-------------|------|-------------|------|-------------|------|-------------|------|-------------|-----|-----------------------|
| | n | % | n | % | n | % | n | % | n | % | |
| 1998 | 161,822 | 25.4 | 193,144 | 30.4 | 188,499 | 29.6 | 78,881 | 12.4 | 13,555 | 2.1 | 635,901 |
| 1999 | 159,097 | 25.6 | 181,931 | 29.3 | 185,311 | 29.8 | 81,281 | 13.1 | 14,252 | 2.3 | 621,872 |
| 2000 | 153,587 | 25.4 | 170,701 | 28.2 | 180,113 | 29.8 | 84,974 | 14.1 | 15,066 | 2.5 | 604,441 |
| 2001 | 153,033 | 25.7 | 159,926 | 26.9 | 178,920 | 30.1 | 86,495 | 14.5 | 16,260 | 2.7 | 594,634 |
| 2002 | 154,426 | 25.9 | 153,379 | 25.7 | 180,532 | 30.3 | 90,449 | 15.2 | 17,336 | 2.9 | 596,122 |
| 2003 | 160,858 | 25.9 | 156,931 | 25.3 | 187,214 | 30.1 | 97,386 | 15.7 | 19,080 | 3.1 | 621,469 |
| 2004 | 166,166 | 26.0 | 159,984 | 25.0 | 190,550 | 29.8 | 102,228 | 16.0 | 20,793 | 3.3 | 639,721 |
| 2005 | 166,975 | 25.9 | 164,348 | 25.4 | 188,153 | 29.1 | 104,113 | 16.1 | 22,246 | 3.4 | 645,835 |
| 2006 | 173,337 | 25.9 | 172,642 | 25.8 | 189,407 | 28.3 | 110,509 | 16.5 | 23,706 | 3.5 | 669,601 |
| 2007 | 175,589 | 25.4 | 182,570 | 26.5 | 191,124 | 27.7 | 115,380 | 16.7 | 25,350 | 3.7 | 690,013 |
| 2008 | 180,662 | 25.5 | 192,959 | 27.2 | 192,450 | 27.2 | 116,218 | 16.4 | 26,419 | 3.7 | 708,708 |
| Ratio 2008/1998 | 1.12 | | 1.00 | | 1.02 | | 1.47 | | 1.95 | | 1.11 |

Hyperglycemia and Adverse Pregnancy Outcomes Study

The HAPO study¹⁹ was a multi-centre, ethnically diverse, observational study carried out in 15 centres in nine countries, including the USA, Canada, the UK (Belfast and Manchester), Australia, Israel, Thailand, Barbados, the Netherlands, Hong Kong and Singapore. The aim of HAPO was to determine ‘what level of glucose intolerance during pregnancy, short of diabetes, is associated with the risk of adverse outcome?’²⁸ All recruits had a 75-g OGTT, and those who were diabetic (1.7%) were removed from the study, for treatment. Diabetes was defined as FPG > 105 mg/dl (5.8 mmol/l – the NDDG criterion) or 2 hours > 200 mg/dl (11.1 mmol/l – the WHO criterion).⁵ Women were also removed if they had a FPG over 5.8 mmol/l, a random PG over 8.9 mmol/l, or had hypoglycaemia (defined as a PG < 2.5 mmol/l). This resulted in 2.9% being removed from the study, leaving 23,316 women who were then followed up without their attending doctors being aware of their results, so that treatment was as usual.

The primary outcomes were birthweight (above 90th centile for gestational age), delivery by section, neonatal hypoglycaemia, and cord-blood C-peptide as an indicator of fetal hyperinsulinaemia. Secondary outcomes included shoulder dystocia or birth injury, need for neonatal intensive care, premature delivery (before 37 weeks), and pre-eclampsia. Details of the protocol have been published.²⁹

In effect all the outcomes reflect fetal insulin levels. Birthweight reflects the number of big babies, some of whom will be entirely normal large babies, while others will have the ‘macrosomic’ syndrome. In an ideal world, there would have been a way

of distinguishing between these groups. Head circumference might be one way.

Birth by section reflects size, fetal well-being and local practice. The percentage born by section ranged from 8.6% to 23.5% amongst centres. Neonatal hypoglycaemia in GDM usually reflects both fetal insulin and treatment, but one of the strengths of the HAPO study was that glucose levels were not disclosed and so the results represent the natural history. Cord blood C-peptide, while not being an outcome in the usual sense of the word, could be regarded as the outcome measure which most closely reflects fetal insulin production.

The HAPO investigators reported the headline results as dichotomies, such as above or below 90th percentiles, but they also ran the data through models as continuous variables.

The HAPO investigators divided women into seven glucose categories, as shown in *Tables 2–4*.

The FPG 4.8–4.9 and 5.6–5.7 ranges are narrower than the others. (These bands have a width of 0.2 mmol/l, the others of 0.3 mmol/l.) This is because of rounding effects from the 5 mg/dl groups.

The upper cut-off of FPG of over 5.8 mmol/l was chosen ‘for ethical or safety reasons’. It is the NDDG threshold value for GDM, dating back to 1979³⁰ and is higher than the threshold of 5.3 mmol/l advocated by the ADA³¹ which was based on the recommendation from the Fourth International Workshop.³²

The small numbers in the categories 6 and 7 meant that numbers of some outcomes were small, and

TABLE 2 The HAPO glycaemia categories – fasting

| Category | Fasting (mmol/l) | Number in category (23,225 total) | % in categories | OR for cord blood C-peptide above 90th PC (95% CI) |
|----------|------------------|-----------------------------------|-----------------|--|
| 1 | <4.2 | 4043 | 17 | 1.0 |
| 2 | 4.2–4.4 | 7501 | 32 | 1.41 (1.15 to 1.74) |
| 3 | 4.5–4.7 | 6168 | 27 | 1.75 (1.42 to 2.15) |
| 4 | 4.8–4.9 | 2741 | 12 | 2.36 (1.88 to 2.97) |
| 5 | 5.0–5.2 | 1883 | 8 | 3.62 (2.87 to 4.58) |
| 6 | 5.3–5.5 | 672 | 3 | 4.46 (3.36 to 5.93) |
| 7 | 5.6–5.7 | 217 | 1 | 7.65 (5.17 to 11.32) |

PC, percentile.

TABLE 3 The HAPO glycaemia categories – 1-hour

| Category | 1-hour post OGTT (mmol) | % in 1-hour categories |
|----------|-------------------------|------------------------|
| 1 | ≤5.8 | 18 |
| 2 | 5.9–7.3 | 32 |
| 3 | 7.4–8.6 | 26 |
| 4 | 8.7–9.5 | 12 |
| 5 | 9.6–10.7 | 8 |
| 6 | 10.8–11.7 | 3 |
| 7 | >11.8 | 1 |

TABLE 4 The HAPO glycaemia categories – 2-hour

| Category | 2-hour OGTT (mmol) | Number in category (23,217 total) | % in categories |
|----------|--------------------|-----------------------------------|-----------------|
| 1 | <5.0 | 4264 | 18 |
| 2 | 5.1–6.0 | 7422 | 32 |
| 3 | 6.1–6.9 | 5864 | 25 |
| 4 | 7.0–7.7 | 3025 | 13 |
| 5 | 7.8–8.7 | 1720 | 7 |
| 6 | 8.8–9.8 | 690 | 3 |
| 7 | >9.9 | 232 | 1 |

confidence intervals (CIs) for the relative risks of clinical neonatal hypoglycaemia were very wide.

In brief, the results for birthweight, delivery by section, pre-eclampsia and shoulder dystocia were linearly related to glucose category.

Correlations amongst the fasting and post-load glucose levels were quite low – 0.38 for FPG and 1-hour PG and 0.3 for FPH and 2-hour PG. No one measure provided a stronger predictor of primary outcomes, except for 1-hour PG and neonatal hypoglycaemia; FPG and 2-hour PG were not significant predictors after adjustment for confounders. For secondary outcomes, premature delivery, a need for neonatal intensive care unit (NICU), and hyperbilirubinaemia were related to 1-hour and 2-hour PG but not to FPG.

That no one glucose measure is better than the others, does raise the question whether we could rely on FPG alone. Jovanovic (2002)³³ has been reported as arguing that the FPG is as useful, or perhaps more useful, than the post-OGTT levels.

The only non-linear relationship was in neonatal hypoglycaemia, where the risk increased sharply in the highest band of FPG. Relative risks (RRs),

taking the lowest band as 1.0, were for successive bands 0.9, 0.9, 1.0, 1.2, 1.0 and 2.0 (rounded to one decimal place). However the overall frequency of neonatal hypoglycaemia was low (2.1%) and the 95% CI around the RR for the top band was 0.97 to 4.05. The frequency of neonatal hypoglycaemia ranged quite widely amongst centres – from 0.3% to 6.4%. The definition was one of symptoms noted in the record, or treatment with a glucose infusion, or a laboratory record of a PG of 1.7 mmol/l or less in the first 24 hours, or of 3.5 mmol/l or less after 24 hours.

There was also a slight divergence from linearity in birthweight and cord serum C-peptide for the highest band of FPG only, but not enough to be significant, with the odds ratios (ORs) for the highest band overlapping with band 6.

Large differences were seen when comparing the extremes of the range. The proportions with birthweight above the 90th percentile (for offspring of non-GDM women) were 5% in the lowest glucose band and 26% in the highest. For birth by caesarean section, the figures were 13% and 28%. It is worth remembering that the medical attendants were blinded to the levels, so the increase in section rates was not due to the diagnosis itself, as was

reported from the Toronto study by Naylor *et al.* (1996).⁹

A later paper from HAPO³⁴ reported that there were also continuous relationships between maternal glycaemia and neonatal adiposity by skinfold or percentage body fat at birth. There were again large differences across the glucose bands. For example, the proportion of infants with sum of skinfolds above the 90th percentile ranged from 5% in the lowest band of FPG, to 26% in the highest. Interestingly, the ORs showed a slightly greater spread (1.0–4.7 in model 2) with FPG, than with 1-hour (range 1.0–3.6) and 2-hour (range 1.0–3.6). However, overall, the same linearities were seen as in the first paper.

The HAPO study collected head circumference, and could use that to distinguish between large healthy babies and macrosomic ones, but this does not yet seem to have been done.

So we have a continuum of risk with no threshold which could divide women into those with HGP, and those without. The main HAPO paper¹⁹ summarises the problem as follows:

‘Lack of clear thresholds for risk and the fact that the four primary outcomes are not necessarily of equal clinical importance make direct translation of our results into clinical practice challenging.’

The HAPO study measured glycated haemoglobin (HbA_{1c}) at the time of the OGTT, and found a rise by gestational age (*Table 5*).³⁵

The investigators also found clear differences in HbA_{1c} amongst women who had to be unblinded because PG levels exceeded the threshold:

- blinded 4.75%
- unblinded because FPG only high 5.32% (0.5%)
- unblinded because 2-hour PG only high 5.14% (0.69%)
- unblinded because both FPG and 2-hour high 6.07% (0.83%).

Much debate has followed the HAPO study. An immediate editorial by Ecker and Greene (2008)³⁶ advised caution against a shift towards treating mild degrees of hyperglycaemia.

One of the HAPO investigators, Boyd Metzger (reported in *Endocrine Today* December 2008),³³ summarised the problem thus:

TABLE 5 HbA_{1c} by gestational age: HAPO data

| Gestation (weeks) | HbA _{1c} (SD) |
|-------------------|------------------------|
| 24–25 | 4.65% (0.43%) |
| 28–29 | 4.75% (0.46%) |
| 31–32 | 4.92% (0.42%) |

‘What is a challenge is to decide how much increase in risk is the point at which treatment should be initiated and what is the hope and expectation for the treatment to reduce those risks ...’

In these situations, cost-effectiveness analysis may help. A study by Lee *et al.* (2008), published only in abstract meantime,³⁷ compared the cost-effectiveness of intervening in HAPO categories 3, 4 and 5 based on the 2-hour PG. It concluded that from a US perspective, intervening in groups 3 and 4 was unlikely to be cost-effective, taking a cost per QALY of < \$50,000 as the upper limit of cost-effectiveness.

Other studies on the continuum versus threshold theme

Since our last HTA report,³ a number of other studies have been published which examine HGP at sub-GDM levels. Time constraints do not allow a comprehensive review of all such studies, but, as will be seen below, they tend to support the HAPO continuum conclusions.

Ferrara *et al.* (2007)³⁸ used the massive Kaiser Permanente database for an observational study to examine the outcomes of pregnancy in the group of women who met the ADA criteria but not the NDDG ones. They had 45,245 pregnancies to study, after excluding GDM by NDDG criteria. They then identified newborns with macrosomia (over 4500 g), neonatal hypoglycaemia, or hyperbilirubinaemia and took random samples of 600 from each group and another 1000 control babies. Data on the 50-g GCT screening tests were extracted from records by researchers blinded to outcomes.

Ferrara *et al.* divided women into four groups:

- normal 50-g GCT
- abnormal GCT (> 7.8 mmol/l) but normal subsequent 100-g OGTT
- abnormal GCT and one OGTT level abnormal by ADA standards

- abnormal GCT and two or more OGTT levels abnormal.

Because mothers of macrosomic babies tended to be older, more parous, more likely to deliver late, and have higher pre-pregnancy BMIs, the results were adjusted to control for these and other factors.

The results showed that mothers of macrosomic babies were more likely to have had abnormal GCTs – 18% abnormal versus 13% on mothers having non-macrosomic babies. (Note an important finding – 82% of mothers of macrosomic babies had normal GCT, and 13% of mothers with normal GCT had macrosomic babies.)

The results for the four groups were as follows, taking those with normal GCT as the reference. *Table 6* shows the ORs for macrosomia.

Despite the large size of the study, CIs are wide.

Amongst those with an abnormal GCT, FPG and 1-hour OGTT PG were stronger predictors of macrosomia than the 2-hour or 3-hour levels.

The key message for our purposes is that the group below the NDDG threshold have an increased risk of macrosomia.

Cheng *et al.* (2007)³⁹ looked at results by bands of GCT results. The usual threshold for abnormality is 140 mg/dl (7.8 mmol/l) but some experts suggest it should be lowered to 130 mg/dl (7.2 mmol/l). Cheng *et al.* divided results into four groups, and obtained the results in *Table 7*.

These differences are small, but again show a continuum. The authors did not give confidence intervals but these have been calculated for this report, rounded to one decimal place.

Several groups have studied the ‘intermediate’ groups, these being women who do not meet the criteria for GDM, but who have had abnormal screening tests. Dodd *et al.* (2007)⁴⁰ compared women whose OGTT results were above normal but below diabetes (e.g. fasting 5.5 mmol/l to 7.0 mmol/l) with those whose results were normal, and found increases in pre-eclampsia, birthweight, shoulder dystocia and neonatal hypoglycaemia.

Di Cianni *et al.* (2007)⁴¹ looked at the group with only one abnormal result in an OGTT (following an abnormal GCT). Nineteen per cent of women fell into this group. Di Cianni *et al.* then divided them into those whose single abnormal results were the FPG, the 1-hour PG, or the later ones. They found metabolic differences with those with only elevated FPG likely to have secretory capacity

TABLE 6 Odds ratios for macrosomia

| Group | OR | 95% CI |
|-----------------------------------|-----|--------------|
| Normal GCT | 1.0 | |
| Abnormal GCT, normal OGTT | 0.9 | 0.57 to 1.31 |
| One abnormal OGTT PG | 2.0 | 1.15 to 3.45 |
| Two or more abnormal OGTT results | 2.7 | 1.2 to 6.0 |

TABLE 7 Outcomes by GCT bands

| | < 120 mg/dl (6.6 mmol/l) | 120–129 mg/dl (6.7–7.1 mmol/l) | 130–139 mg/dl (7.2–7.7 mmol/l) | ≥ 140 mg/dl (7.8 mmol/l) |
|---|-----------------------------|-----------------------------------|-----------------------------------|-----------------------------|
| % with birthweight over 3999 g (95% CI) | 10.8 (10.2 to 11.4) | 11.4 (9.4 to 13.2) | 12.5 (10.6 to 14.45) | 13.6 (12.1 to 15.1) |
| Delivery by section (%; 95% CI) | 11.3 (10.7 to 12.0) | 13.8 (11.8 to 15.8) | 14.5 (12.5 to 16.5) | 15.9 (14.6 to 17.2) |
| Hypoglycaemia (%; 95% CI) | 1.6 (1.3 to 1.9) | 1.8 (1.04 to 2.6) | 2.0 (1.2 to 2.8) | 2.1 (1.47 to 2.7) |
| Pre-eclampsia (%; 95% CI) | 4.0 (3.1 to 4.9) | 4.6 (3.4 to 5.8) | 5.3 (5.0 to 5.6) | 6.2 (5.2 to 7.2) |
| Values are percentages and 95% CIs. | | | | |

problems, whereas those with only 1-hour raised have more insulin resistance.

Biri *et al.* (2009)⁴² in Turkey also examined results in intermediate groups, comparing those with normal GCTs with those with abnormal GCT but normal OGTT, and thirdly those with one abnormal OGTT result. Macrosomia was seen in 6% of the normal group, and in 8% and 13% of the other groups. In Malaysia, **Tan *et al.* (2009)**⁴³ also looked at outcomes in an abnormal GCT but normal OGTT group, and found that some adverse outcomes were increased, though increases were small.

Jensen *et al.* (2008)⁴⁴ from Denmark found a linear relationship similar to HAPO in women with 2-hour 75-g OGTT levels under 9 mmol/l (i.e. after excluding those with GDM) for shoulder dystocia, caesarean section, and macrosomia, but not for hypoglycaemia.

Recent reviews

The US Preventive Services Task Force⁴⁵ reviewed its policy on screening for GDM in 2008, and concluded that there was insufficient evidence to make any recommendation.

The German equivalent of NICE, the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)⁴⁶ has recently reviewed screening for GDM, and has also concluded that there is insufficient evidence to make a recommendation.

National Institute for Health and Clinical Excellence

NICE has produced, or updated, two relevant guidelines, *Antenatal Care*⁴⁷ and *Pregnancy in Diabetes*.² The sections on gestational diabetes were developed in collaboration. Both guidelines were produced before the publication of HAPO. They also preceded most of glibenclamide studies (they had two RCTs and four observational studies) and all of the metformin ones. They assumed that the 75-g OGTT was the gold standard for the diagnosis of GDM, and used the WHO criteria (FPG 7.0 mmol/l or over, and/or 2-hour PG over 7.8 mmol/l).

The guidelines assumed, based on their review of both clinical effectiveness and cost-effectiveness, that screening would be selective, based on:

- BMI > 30
- a previous baby weighing over 4500 g
- previous GDM
- diabetes in a first degree relative
- high-risk ethnicity.

However they excluded age, on the grounds that:²

‘Advanced maternal age should not be used as a risk factor because this would result in most pregnant women requiring an OGTT.’

(Section 4.1)

It is likely that they were thinking of the ADA age threshold of 25 years.

The antenatal guidelines recommended that none of urine glucose, random BG, FPG and the 50-g GCT should be used. They had reviewed the evidence for these and regarded them as having shortcomings. However they did not review the evidence on the 75-g OGTT, which they took to be a perfect test. This was partly because, pre-HAPO, the Guidelines Development Groups (GDGs) were thinking in terms of a condition defined by the OGTT.

The guidelines were supported by thorough cost-effectiveness modelling, using a newly developed model which looks very good. A wide range of screening options were examined, including combinations of selection by the ADA risk factor or universal screening, different glucose screening tests, with or without the OGTT. Issues with the modelling include:

- The assumptions on benefits of treatment were based on ACHOIS, which included women with glucose levels which were mainly restricted to IGT, by excluding women with 2-hour PG over 11 mmol/l, though FPG of up to 7.7 mmol/l was allowed. So ACHOIS recruited women in effect with what would be IGT outwith pregnancy, but which was then defined by WHO as GDM, but excluded those with the highest glucoses at screening. The implication is that the ACHOIS outcomes might be less severe in the untreated group than would be the case if the whole range of hyperglycaemia in pregnancy was included.
- In the absence of data on metformin, they assumed that the clinical effects would be similar to glibenclamide (including the frequency of hypoglycaemia, which seems incorrect) but that the cost would be less.

- It was assumed that the 75-g OGTT had perfect sensitivity and specificity.
- The WHO criteria were used, so in effect the modelling related to the HAPO 2-hour categories 5, 6 and 7.
- Some assumptions were based on single studies, for example the sensitivity and specificity of FPG were based on the Brazilian study of Reichelt *et al.* (1998).⁴⁸

The cost-effectiveness analysis concluded that a strategy based on risk factors (i.e. the ADA criteria, which include age) followed by the OGTT was the best, except for high-risk ethnic groups, where ethnicity alone followed by the OGTT was considered appropriate.

The cost-effectiveness analysis concluded that glibenclamide treatment was usually as good as insulin, and, being cheaper, was more cost-effective. They do not seem to have carried out an analysis of the marginal cost-effectiveness of insulin in glibenclamide failures, probably due to shortage of data at the time.

The GDG expressed some caution about the use of glibenclamide:²

‘Health economic analysis has demonstrated that glibenclamide is cost-effective, but the clinical evidence comes from a healthcare setting outside the UK, and the GDG’s view is that the acceptability to women of treating gestational diabetes with glibenclamide has not yet been demonstrated in the NHS healthcare setting.’

(Section 4.3)

The GDG did not produce any evidence that glibenclamide would not be acceptable, nor any rationale for why glibenclamide would not be effective in controlling hyperglycaemia in British women. They noted that data on metformin would become available. The recommendations were that treatment should start with diet and physical activity, and if those were insufficient, oral hypoglycaemics or insulin could be used as appropriate. There is now more evidence on oral agents.

Key questions for this review

The need for an update of the previous review³ for NSC arises for several reasons:

- Overweight and obesity are increasing in the population, which will lead to an increase in the frequency of GDM and HGP.
- Maternal age at birth is also increasing, which again will raise the incidence of HGP (though some of this will be due to weight gain with age).
- We have better evidence on treatment from the ACHOIS¹⁸ and MFMUN²⁰ trials.
- We now have the HAPO results.¹⁹

The key questions are:

1. After HAPO and similar studies, what level of HGP do we need to detect? This depends on the level at which we intervene to reduce adverse consequences. At the high end of PG, there will be definite benefits to the baby and the benefits will outweigh the harms and inconveniences. But at the lower end of the hyperglycaemia distribution (which could be just above the upper limit of normal) the harms and inconveniences may outweigh the benefits, if any. What we need to do is decide where along the continuum of glucose, the ‘switching point’ is. Below this point intervention would result in a net disbenefit, above it intervention would produce overall benefit.
2. Having decided the level at which to intervene, which screening test should be used?
3. Should there be universal PG testing, or selection by risk factors so that only a proportion of women proceed to blood testing?
4. Are oral glucose lowering drugs effective and safe? If so, what should the treatment pathway be? Lifestyle, then oral agents, then insulin, as required to control PG? If oral drugs are clinically as effective as insulin in most cases, their availability will make treatment cheaper and easier and more acceptable to women. There have also been, since the NICE reviews, new studies of lifestyle measures.
5. What are the research needs now? Should the HTA programme seek to commission any more primary research? NICE suggested that

‘a multi-centre trial is required to test existing screening techniques in the UK’.

The continuum problem

As mentioned above, the HAPO study¹⁹ found linear associations between glucose levels and adverse outcomes. That makes deciding on cut-offs for intervention difficult. The clinical approach might be to intervene at a level which seemed ‘clinically reasonable’ perhaps based on the RR – for example, choosing the level at which adverse events increased by 50%. That would be simply a concealed arbitrary clinical decision.

An economic approach would be to model the cost per QALY of intervening at different thresholds, using the affordability threshold use by NICE of up to £30,000 per QALY. However, although the NICE threshold has become the norm in the UK, NICE does not always abide by it, and the figure of £30,000 in effect represents a concealed arbitrary NICE decision.

One option would be to choose a threshold cost per QALY well below the £30,000 NICE one, and by further modelling (outwith the scope of this review, but which could be done by those who did the modelling for NICE) identify a number of screening and treatment strategies which gave a cost per QALY of under, say, £20,000. Note that many of the options identified by the NICE modellers were well under that threshold.

Having identified such screening strategies, the effect on numbers to be screened could then be estimated, and the practicalities of screening and treating such numbers could be considered. This approach would in effect be a pragmatic mixture of cost-effectiveness analysis and clinical judgement.

The alternative would be to postpone a decision until a randomised trial, with cost-effectiveness analysis, of intervention at different thresholds had been done.

Chapter 2

Treatment of hyperglycaemia in pregnancy: oral glucose-lowering drugs versus insulin

The recent trials

Despite the recognition that hyperglycaemia in pregnancy is associated with both maternal and neonatal adverse outcomes, there has been uncertainty about the benefits of treating this. However, two studies undertaken during recent years have contributed to our understanding of the benefits associated with intervention.

The Australian Carbohydrate Intolerance Study in Pregnant Women trial

Crowther *et al.* undertook a randomised controlled trial among 1000 women diagnosed with gestational diabetes at 24–34 weeks' gestation between September 1993 and June 2003.¹⁸ Women recruited to the study attended antenatal clinics at participating hospitals in Australia and the UK.

Women with:

- one or more risk factors for gestational diabetes *or*
- a positive 50-g oral GCT (1-hour post-test glucose level of at least 7.8 mmol/l) underwent a 75-g oral GCT at 24–34 weeks gestation.

To be eligible for inclusion (see *Table 8*), women had to have:

- a PG level of less than 7.8 mmol/l after an overnight fast *and*
- a 2-hour post-test glucose level of 7.8–11.0 mmol/l.

Hence diagnosis was by the 2-hour level, which needs to be borne in mind when we come to discuss the possibility of screening using FPG.

Women with more severe hyperglycaemia were excluded, as were women previously diagnosed with gestational diabetes and those with an active chronic systemic disease.

Women were randomised to receive dietary advice, BG monitoring and insulin therapy as required

(the intervention group) or routine care (the control group). Four hundred and ninety and 510 women were allocated to the intervention and control groups respectively.

Women allocated to the intervention group were informed that they had IGT of pregnancy. They received dietary advice from a qualified dietician and instructions on how to self-monitor glucose levels to assess if their hyperglycaemia was adequately controlled:

- fasting glucose levels of 3.5–5.5 mmol/l
- pre-prandial glucose levels of no more than 5.5 mmol/l
- 2-hour PPG levels of no more than 7.0 mmol/l.

Insulin therapy was commenced if there were two capillary-blood glucose levels outwith the above during a 2-week period. Insulin therapy was adjusted based on the results of ongoing monitoring. In the intervention group, 20% needed insulin.

Women allocated to the control group were informed that they did not have gestational diabetes, and received standard care. However, if perceived to be clinically necessary, attending clinicians could refer women for additional assessment for gestational diabetes.

The two groups were broadly similar, although women in the intervention group:

- were slightly older
- had a higher mean BMI
- were less likely to be Caucasian.

Fasting blood glucose levels prior to the glucose tolerance test were 4.8 [standard deviation (SD) 0.7] mmol/l and 4.8 (SD 0.6) mmol/l among intervention and control group mothers respectively. The median 2-hour post-test levels were 8.6 mmol/l (interquartile range: 8.1 to 9.3) and 8.5 mmol/l (interquartile range: 8.1 to 9.1) among intervention and control group mothers

respectively. No statistical analyses of the baseline differences between the groups were reported.

The primary outcome for the trial was the rate of serious perinatal complications defined as one or more of the following:

- death
- shoulder dystocia
- bone fracture
- nerve palsy.

The rate of serious perinatal complications was significantly lower among children born to mothers in the intervention group compared with children born to control group mothers (1% vs 4%; $p = 0.01$). The number needed to treat to prevent a serious perinatal complication was calculated as 34 (95% CI 20 to 103). The largest number of outcomes was from shoulder dystocia, 16 of 23 (64%) serious complications. The assessors of shoulder dystocia do not appear to have been blinded to treatment group. The authors state that 'the presence and severity of shoulder dystocia was assessed using a checklist by the care-giver at birth'.

With respect to secondary outcome measures, children born to mothers in the intervention group were significantly less likely to be large for gestational age (LGA – 13% vs 22%; $p < 0.001$) or macrosomic (10% vs 21%; $p < 0.001$) compared with children born to mothers in the control group. Antenatal pre-eclampsia was also less common among intervention group mothers compared with control group mothers (12% vs 18%; $p = 0.02$). Mothers in the control group gained 9.8 kg and in the intervention group, 8.1 kg ($p < 0.001$).

However, children born to mothers in the intervention group were more likely to be admitted to the neonatal nursery (71% vs 61%; $p = 0.01$). Despite this, intervention group children were no more likely to be hypoglycaemic, to have suffered seizures or to have respiratory distress syndrome. Intervention group women were more likely to undergo induction of labour (39% vs 29%; $p < 0.001$) although caesarean section rates were not significantly different. As a consequence, the children of mothers in the intervention group were born at a slightly earlier gestational age (median 39 vs 39.3 weeks – not statistically significant).

The investigators suggested that these observations may reflect attending physicians' awareness that intervention group women had hyperglycaemia.

They also suggested that the earlier gestational age at birth may have contributed to the reduction in serious perinatal complications.

In conclusion, the authors state '... that the treatment of gestational diabetes in the form of dietary advice, blood glucose monitoring and insulin therapy as required for glycaemic control reduces the rate of serious perinatal complications, without increasing the rate of caesarean delivery'.¹⁸

The Maternal and Fetal Medicine Units Network trial

The Maternal and Fetal Medicine Units Network (MFMUN) undertook a multi-centre randomised trial comparing diet and insulin therapy versus no specific treatment among women with mild hyperglycaemia in pregnancy. The trial methodology⁴⁹ and results have been published.²⁰

All women attending participating hospitals were subjected to a screening 50-g GCT between 24–29 weeks gestation. Women with a 1-hour glucose level in the range 135–199 mg/dl (7.5–11.0 mmol/l) underwent a diagnostic 3-hour oral 100-g OGTT. To be eligible for inclusion in the trial, women had to have:

- a fasting glucose level of less than 95 mg/dl (5.3 mmol/l), and
- two of the three post-glucose load determinations exceeding thresholds established by the Fourth International Workshop–Conference on Gestational Diabetes:³²
 - 1 hour: greater or equal to 180 mg/dl (10.0 mmol/l)
 - 2 hours: greater or equal to 155 mg/dl (8.6 mmol/l)
 - 3 hours: greater or equal to 140 mg/dl (7.8 mmol/l).

Women in the intervention group received formal nutritional counselling, diet therapy and instruction in glucose self-monitoring and insulin if required. Insulin therapy was recommended for women in which the majority of:

- fasting levels were 95 mg/dl (5.3 mmol/l) or greater *or*
- 2-hour post-prandial levels were greater than 120 mg/dl (6.7 mmol/l)

after 1 week of diet therapy.

The primary outcome measure for the trial was a composite of:

- perinatal mortality *and*
- morbidities associated with maternal hyperglycaemia – stillbirth, neonatal mortality, hypoglycaemia, hyperbilirubinaemia, neonatal hyperinsulinaemia and birth trauma.

The investigators aimed to recruit 475 women to both the intervention and the control groups.

Four hundred and eighty-five and 473 women were recruited to the treatment and control groups respectively. There was no significant difference in the primary outcome between the groups [32.4% (149/460) vs 37.0% (163/440); $p = 0.14$].

However, differences between the groups were reported for the following (intervention vs control group):

- mean birthweight (3302 ± 502 g vs 3408 ± 589 g; $p = 0.0005$)
- neonatal fat mass (427 ± 198 g vs 464 ± 222 g; $p = 0.003$)
- birthweight more than 4000 g [5.9% (28/477) vs 14.3% (65/454); $p = 0.0001$]
- LGA [7.1% (34/477) vs 14.5% (66/454); $p = 0.0003$]
- shoulder dystocia [1.5% (7/476) vs 4.0% (18/455); $p = 0.019$]
- caesarean section rates [26.9% (128/476) vs 33.8% (154/455); $p = 0.021$].

(The \pm figures are SDs.)

Crowther *et al.* (2005)¹⁸ also reported that children born to women in the treatment group within their study had a lower mean birthweight and

were less likely to be LGA. However, they reported no statistically significant differences between the intervention and control groups with respect to rates of shoulder dystocia and delivery by caesarean section.

Table 8 shows the eligibility criteria of the two trials.

Summary

These two trials aimed to recruit women with differing levels of hyperglycaemia, although women in the trial undertaken by Crowther *et al.* (2005)¹⁸ would appear, in general, to have had levels that would make them eligible for the Landon trial^{49,50} (e.g. the mean fasting glucose was 4.8 mmol/l in both the intervention and control group mothers).

The primary outcomes reported in these trials were different making it difficult to compare their results (Table 9) Nevertheless, Crowther *et al.* (2005)¹⁸ reported a statistically significant reduction in the primary outcome of serious perinatal complication among infants born to mothers in the intervention group compared with those born to mothers in the control group. However, Landon *et al.* (2008)⁵⁰ reported no statistically significant difference between the intervention and control groups with respect to the primary outcome.

As discussed previously, women in the trial undertaken by Landon *et al.* (2007/8)^{49,50} may have had lower levels of hyperglycaemia than women recruited by Crowther *et al.* (2005).¹⁸

The findings of these trials suggest that women with higher levels of hyperglycaemia, and their infants, derive more benefit from treatment than women with relatively low levels of hyperglycaemia.

TABLE 8 Eligibility criteria

| | Gestation at assessment | Method of assessment | Fasting glucose (venous plasma) | OGTT (venous plasma) |
|---|-------------------------|----------------------|----------------------------------|---|
| Crowther <i>et al.</i> (2005)¹⁸ | 24–34 weeks | 75-g OGTT | Less than 7.8 mmol/l (140 mg/dl) | 2 hours: 7.8–11.0 mmol/l (140–199 mg/dl) |
| Landon <i>et al.</i> (2008)⁴⁹ | 24–29 weeks | 100-g OGTT | Less than 5.3 mmol/l (95 mg/dl) | 1 hour: 10.0 mmol/l or more (180 mg/dl or more) 2 hours: 8.6 mmol/l or more (155 mg/dl or more) 3 hours: 7.8 mmol/l or more (140 mg/dl or more) |

TABLE 9 Study outcomes

| | Primary outcomes | Secondary outcomes |
|--|---|--|
| Crowther et al. (2005)¹⁸ | <p><i>Infants:</i></p> <p>A composite measure of serious perinatal complications. One or more of the following:</p> <p>Death</p> <p>Shoulder dystocia</p> <p>Bone fracture</p> <p>Nerve palsy</p> <p><i>Mothers:</i></p> <p>Induction of labour</p> <p>Caesarean section rate</p> <p>Maternal health (SF-36)</p> <p>Maternal anxiety (Spielberger State–Trait Anxiety Inventory)</p> <p>Depression (Edinburgh Postnatal Depression Scale)</p> | <p><i>Infants:</i></p> <p>Components of the primary outcome</p> <p>Gestational age at birth</p> <p>Birthweight</p> <p><i>Mothers:</i></p> <p>Number of prenatal visits to a health professional</p> <p>Mode of birth</p> <p>Weight gain during pregnancy</p> <p>Number of antenatal admissions</p> <p>Pregnancy induced hypertension</p> |
| Landon et al. (2008)⁴⁹ | <p><i>Infants:</i></p> <p>A composite measure of:</p> <p>Perinatal mortality</p> <p>Stillbirth</p> <p>Neonatal mortality</p> <p>Hypoglycaemia</p> <p>Hyperbilirubinaemia</p> <p>Neonatal hyperinsulinaemia</p> <p>Birth trauma</p> | <p><i>Infants:</i></p> <p>Macrosomia</p> <p>LGA</p> <p>Neonatal ponderal index</p> <p>Brachial plexus injury</p> <p>Fetal distress</p> <p>Respiratory distress syndrome</p> <p><i>Mothers:</i></p> <p>Caesarean section/operative delivery</p> <p>Maternal weight gain</p> <p>Pre-eclampsia</p> <p>Length of stay</p> |

SF-36, Short form questionnaire-36 items.

Treatment of hyperglycaemia in pregnancy: oral drugs versus insulin

The principal aims of treating hyperglycaemia in pregnancy are to reduce mortality and morbidity among women and their children.² Treatment has typically involved:^{51–56}

- dietary modification \pm exercise *and*
- pharmacological treatment for women unable to maintain their glucose levels within an acceptable range despite dietary modification \pm exercise.

It has been claimed that most women with hyperglycaemia in pregnancy can maintain adequate glycaemic control without

pharmacological therapy.^{2,57} However, others have stated that up to 60% of women will require pharmacological therapy.^{53,56} For those women requiring pharmacological treatment, insulin has traditionally been used.^{51,52,54–56,58–61}

Oral anti-diabetic agents were used during the 1970s and 1980s to treat T2DM and hyperglycaemia in pregnancy.⁵⁸ Following concerns regarding increased perinatal mortality and neonatal hypoglycaemia, they fell out of favour.⁵⁹

However, insulin therapy is not without its drawbacks:

- need for injections which may be unpopular with women,⁵⁶ which may lead to problems with adherence⁵³
- risk of hypoglycaemia⁵⁶
- risk of excessive weight gain⁵⁶

- cost of insulin and the equipment necessary to administer it.⁵⁴

Furthermore, as hyperglycaemia in pregnancy is associated with insulin resistance and reduced insulin secretion, oral agents may have a role.⁵⁶ Therefore, the use of oral anti-diabetic agents has been investigated and debated during recent years.

Metformin reduces gluconeogenesis and improves glucose uptake⁵⁶ by increasing the number, and sensitivity, of glucose receptors to insulin.⁵³ It is not associated with weight gain or hypoglycaemia.⁵⁶ However, metformin is known to cross the placenta.^{58,59,62}

The sulphonylurea drug, glyburide/glybenclamide, acts by stimulating maternal insulin secretion.⁵³ It is claimed that, compared with insulin, it is less likely to cause hypoglycaemia.⁶³ It is uncertain if glyburide crosses the placenta. Some researchers suggest that it does not, whereas others have reported minimal transfer.^{58,59,62} The key point is that, if it does, the level in the fetal circulation is very low. This applies only to glibenclamide and not to other sulphonylureas.

Debate has focused on the effectiveness and safety of oral agents compared with insulin. Jovanovic (2007)⁶⁴ states that maternal PPG levels are a more significant contributor to fetal hyperinsulinaemia and macrosomia than average glucose levels. She claims that both metformin and sulphonylurea drugs do not control PPG levels as effectively as insulin, and concludes: 'Oral hypoglycaemic agents may have enough data to prove that they do not harm the fetus; however, they clearly do not achieve the post-prandial glucose response needed to normalise birthweight'.⁶⁴

However, Coustan (2007)⁵⁸ has concluded: 'Given the available data, glyburide appears to be the best candidate insulin secretagogue for use during pregnancy, since it crosses the placenta little or not at all and benefits the mother directly and the foetus indirectly'. Discussing metformin, he writes: '... data suggest that significant amounts of metformin can cross the placenta ... Because it is unknown whether metformin is therapeutic or deleterious to the foetus, it would seem prudent to obtain further data (perhaps from animal models) before metformin becomes commonly prescribed during pregnancy. At the very least, patients should be counselled about the unknown risks and benefits for the foetus'.

Coetzee (2007),⁶² although supportive of the use of oral hypoglycaemic agents in pregnancy, agrees that caution should be exercised with respect to metformin, stating that long-term follow-up studies of infants born to mothers who have taken the drug are required given that metformin is known to cross the placenta.

Homko and Reece (2006)⁶⁰ conducted a non-systematic review of hypoglycaemic agents during pregnancy. With respect to metformin, they reported:

- There is no evidence of teratogenicity.
- One study which reported that women treated with metformin had a higher prevalence of pre-eclampsia and a high perinatal mortality as compared with women treated with insulin therapy.
- Data regarding the long-term implications of metformin use during pregnancy for offspring are limited.

With respect to sulphonylurea drugs, Homko and Reece (2006)⁵⁹ concluded: 'Based on the currently available data, it would appear that glyburide could be safely and effectively utilised in the management of women with GDM'.

Langer (2006),⁶⁵ in a non-systematic review concluded that: 'Glyburide is a cost-effective, patient friendly, and potentially compliance-enhancing therapy that produces perinatal outcomes in GDM pregnancies comparable to traditional insulin therapy. For GDM patients who require pharmacologic therapy, glyburide is the drug of choice and only patients who fail to achieve glycaemic control should begin insulin therapy'.

Guidance recently published by NICE allows the use of both glibenclamide and metformin in the management of women who develop hyperglycaemia in pregnancy, although it had to be written before the metformin trials had reported, and when only two glibenclamide trials were published. The GDG expressed caution about the use of glibenclamide, as reported in Chapter 1.

Summary

Up to 14% of women may develop hyperglycaemia during pregnancy. A RCT involving women who developed moderate hyperglycaemia during pregnancy demonstrated that treatment to normalise glucose levels led to a significant reduction in serious perinatal complications.¹⁸

However, a second trial which recruited women with relatively lower levels of hyperglycaemia reported no difference between study groups with respect to the primary outcome – a composite of perinatal mortality and neonatal morbidities associated with maternal hyperglycaemia.⁵⁰

Review of evidence on oral drugs

The objective of this section is to assess the risks and benefits of oral glucose lowering drugs compared with insulin in the treatment of hyperglycaemia in pregnancy.

Inclusion criteria

Types of studies

Existing systematic reviews and additional primary studies, which these reviews had not included.

Types of participants

Women developing hyperglycaemia for the first time during their pregnancy. All trials targeting hyperglycaemia were included but the definition of 'hyperglycaemia' in each trial was noted.

Types of interventions

Studies had to compare the use of oral agents to insulin (any type or regimen).

Types of outcomes

The outcomes listed below were considered.

Maternal/obstetric outcomes

Primary outcomes

- Pre-eclampsia/hypertensive complications.
- Caesarean delivery.
- Glycaemic control during pregnancy.
- Hypoglycaemia.

Secondary outcomes

- Induction of labour.
- Maternal weight.
- Post-partum glucose tolerance.
- Acceptability of treatment.
- Maternal anxiety.
- Depression.
- Health status.

Child/neonatal outcomes

Primary outcomes

- Hypoglycaemia.
- Birthweight.
- Macrosomia (birthweight ≥ 4000 g).

- LGA (> 90th percentile).
- Perinatal mortality.
- Birth trauma (e.g. shoulder dystocia, bone fracture, nerve palsy).

Secondary outcomes

- Hyperbilirubinaemia/need for phototherapy.
- SGA (< 10th percentile).
- NICU admission.
- Congenital malformations.
- Respiratory distress.
- 5-minute Apgar score < 7.
- Prematurity.

Search strategy

Databases searches were undertaken in MEDLINE (1996 to January 2009), EMBASE (1996 to December 2008), the Cochrane Library 2008 issue 4 and Web of Science – limited to meeting abstracts only (2000 to January 2009). Details of the search strategies and the flow of studies are shown in Appendix 1. All searches were limited to English language only.

Study selection

Systematic reviews were included if they:

- included studies which considered the treatment of women developing hyperglycaemia in pregnancy (if a review considered women with pre-existing impaired glucose tolerance and/or diabetes as well as hyperglycaemia in pregnancy, the findings should be presented separately)
- considered studies which compared treatment with insulin with oral hypoglycaemic agents
- reported maternal outcomes (e.g. pre-eclampsia, hypoglycaemia, weight gain, glycaemic control) and neonatal outcomes (e.g. hypoglycaemia, birthweight, macrosomia)
- contained a description of their inclusion criteria
- contained a description of their search strategy
- searched more than one electronic database.

Primary studies (RCTs, observational studies) were included if they:

- considered women developing hyperglycaemia in pregnancy (if studies included women with pre-existing impaired glucose tolerance and/or diabetes as well as hyperglycaemia in pregnancy, the findings should be presented separately)

- compared treatment using insulin with oral hypoglycaemic agents
- reported maternal outcomes (e.g. pre-eclampsia, hypoglycaemia, weight gain, glycaemic control) or neonatal outcomes (e.g. hypoglycaemia, birthweight, macrosomia)
- were published since January 2007, and were not included within any of the systematic reviews selected (of the reviews included, none searched electronic databases beyond January 2007).

We also included studies describing factors associated with failure to achieve adequate maternal glycaemic control on oral hypoglycaemic therapy, since they might identify women who should go straight to insulin. Studies were included if they reported on factors associated with failure to achieve adequate maternal glycaemic control.

We then combined the primary studies that the reviews had identified, and the new ones, in updated meta-analyses.

Quality assessment of studies

The following quality criteria were used for assessing systematic reviews:

- description of inclusion criteria
- details of literature search given
- description of study selection
- description of data extraction
- description of study quality assessment
- study flow shown
- description of study characteristics of individual studies
- quality of individual studies given
- results of individual studies shown
- statistical analysis appropriate.

The following criteria were used for assessing RCTs:

- method of randomisation
- allocation concealment
- blinding
- intention to treat data analysis
- percentage who completed trial
- power calculation
- similarity of groups at baseline.

The following criteria were used for assessing observational studies (cohort studies):

- Is there sufficient description of the groups and the distribution of prognostic factors?
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all important confounding factors?
- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose–response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was follow-up long enough for the outcomes to occur?
- What proportion of the cohort was followed up?
- Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Data synthesis

Data were summarised in tables and in meta-analyses. Continuous data were expressed as weighted mean differences (WMDs) and dichotomous data as relative risks. Random effects models were used (Mantel–Haenszel for risk ratios and inverse variance method for weighted mean differences). Summary statistics were calculated for the most important outcomes and where enough (three or more) similar studies were available. Meta-analyses were done separately for different study types. Heterogeneity was assessed using the chi-squared method.

Results

Three relevant systematic reviews were identified.^{2,54,55} One of these⁵⁴ focused on perinatal outcomes associated with maternal glibenclamide therapy, whereas the other two considered a range of maternal and neonatal outcomes associated with maternal receipt of glibenclamide and other oral agents.

As shown in *Table 10*, only a minority of studies relevant to our objectives were included within each of the previous reviews. Therefore we undertook a new review of primary studies.

We identified a total of 27 primary studies from the three systematic reviews and additional

searches (papers published in full and meeting abstracts), as shown in *Table 10*. There were four RCTs^{66–69} and 11 observational studies^{52,61,70–78} comparing glibenclamide with insulin. Seven observational studies^{63,79–84} examined (predictors of) glibenclamide failure/success. One of the RCTs⁶⁷ also included a group receiving acarbose. There were three RCTs^{85–88} and three observational studies^{56,70,89} comparing metformin with insulin.

The trials in *Table 10* will hereafter be referred to by the name of the first author and year of publication in the figures and text of the results section.

Systematic reviews

Description of reviews

Appendix 2 shows the characteristics of the included reviews. The review by Moretti (2008)⁵⁴ focused on the safety of glibenclamide, while the other two reviews^{2,55} looked at oral anti-diabetic agents in general. All reviews were done for national health agencies (in Canada, the USA or the UK).

Inclusion criteria

All reviews included observational studies as well as RCTs. Glibenclamide, metformin or acarbose were compared with insulin treatment in women with gestational diabetes. The review by Moretti (2008)⁵⁴ focused on perinatal outcomes, while the other two reviews considered a range of maternal and neonatal outcomes.

Methodology

The review by Moretti (2008)⁵⁴ gave details of its search strategy and study flow, but other details of the methodology employed were not reported. Data were summarised in a meta-analysis using ORs, WMDs and a random effects model. There was only a very limited summary of the characteristics of primary studies.

There was a very thorough description of the search strategy of the NICE guideline,² including a large range of databases. The search was restricted to studies published in English. The rest of the methodology was not described in detail, but it was suggested that methodology outlined in the *NICE Guidelines Manual*⁹³ was used. No meta-analysis was carried out and the main data summary was done using narrative descriptions of the included studies, with supplementary information provided in evidence tables.

The review by Nicholson (2009)⁵⁵ also included a thorough literature search of a range of databases. Non-English studies were excluded. Study selection, quality assessment, and data extraction were all done by two independent reviewers. Study flow was shown and criteria for quality assessment were named. A meta-analysis of birthweight was carried out. The rest of the evidence was summarised in tables.

Included studies

Moretti (2008)⁵⁴ included one RCT and eight cohort studies (four prospective and four retrospective). Further details on study design were not reported. The range of patients per study group was 7–268 and treatment was generally started at around 24 weeks of gestation with a typical daily dose of glibenclamide of 5–10 mg. A range of neonatal outcomes were reported.

The NICE guideline² included three RCTs (one with three arms) and three cohort studies. Two RCTs compared glibenclamide with insulin, one compared acarbose with insulin, and one compared metformin with insulin. The three cohort studies compared glibenclamide with insulin. A range of maternal and neonatal outcomes were reported.

The review by Nicholson (2009)⁵⁵ included four RCTs (including one with three arms) and five cohort studies. Three of the RCTs compared glibenclamide with insulin, one compared acarbose with insulin, and one compared metformin with insulin. All the cohort studies compared glibenclamide with insulin. Some details of participant characteristics were reported and a range of maternal and neonatal outcomes was given.

Quality

In the review by Moretti (2008)⁵⁴ inclusion criteria and the literature search were described, but details of much of the remaining methodology were lacking and information on the primary studies was limited. The quality of the primary studies was not described and results were only given for those outcomes that could be meta-analysed.

The NICE guideline² described inclusion criteria and the search strategy, but for most of the remaining methodology it had to be assumed that appropriate methods were used. Studies were summarised narratively rather than more systematic information being provided in tables.

TABLE 10 Primary studies in reviews and from extra searches

| Study | Moretti 2008 ⁵⁴ | NICE guideline 2008 ² | Nicholson 2009 ⁵⁵ | New |
|---|----------------------------|----------------------------------|------------------------------|-----|
| Glibenclamide vs insulin | | | | |
| <i>RCT</i> | | | | |
| Anjalakshi (2007) ⁶⁶ | | | ✓ | |
| Bertini (2005) ⁶⁷ (also acarbose) | | ✓ | ✓ | |
| Langer (2000) ^{68,90} | ✓ | ✓ | ✓ | |
| Ogunyemi (2007) ^{69,91} | | | | ✓ |
| <i>Observational</i> | | | | |
| Coetzee (1986) ⁷⁰ (also metformin) | ✓ | | | |
| Duncan (2005) ⁷¹ (A) | | | | ✓ |
| Fines (2003) ⁷² (A) | ✓ | | | |
| Gilson (2002) ⁷³ (A) | ✓ | | | |
| Goodman (2008) ⁷⁴ (A) | | | | ✓ |
| Holt (2008) ^{52,92} | | | | ✓ |
| Jacobson (2005) ⁷⁵ | ✓ | ✓ | ✓ | |
| Langer (2006) ⁷⁶ (A) | | | | ✓ |
| Patterson (2008) ⁷⁷ (A) | | | | ✓ |
| Ramos (2007) ⁶¹ | | | | ✓ |
| Yogev (2004) ⁷⁸ | | ✓ | ✓ | |
| Glibenclamide failure | | | | |
| Chmait (2004) ⁷⁹ | ✓ | | ✓ | |
| Conway (2004) ⁸⁰ | ✓ | ✓ | ✓ | |
| Kahn (2006) ⁶³ | | | | ✓ |
| Langer (2006) ⁸¹ (A) | | | | ✓ |
| Parrish (2008) ⁸² | | | | ✓ |
| Rochon (2006) ⁸³ | ✓ | | ✓ | |
| Velazquez (2003) ⁸⁴ (A) | ✓ | | | |
| Metformin vs insulin | | | | |
| <i>RCT</i> | | | | |
| Hague (2003) ⁸⁵ (MiG pilot) | | ✓ | | |
| Moore (2007) ⁸⁶ | | | | ✓ |
| Rowan (2008) ^{87,88} (MiG) | | | ✓ | |
| <i>Observational</i> | | | | |
| Balani (2008) ⁸⁹ (A) | | | | ✓ |
| Tertti (2008) ⁵⁶ | | | | ✓ |
| A, abstract only. | | | | |

The review by Nicholson (2009)⁵⁵ was rated as being high quality and fulfilled all the quality criteria specified.

Results and conclusions of reviews

Of 27 primary RCTs and cohort studies now available, the reviews included between six and nine (with an overlap of only three used in all reviews). The reviews reported outcomes for pre-eclampsia, caesarean delivery, glycaemic control during pregnancy, maternal hypoglycaemia, neonatal hypoglycaemia, hyperbilirubinaemia, birthweight, macrosomia, LGA and SGA, perinatal mortality, neonatal intensive care admission, birth

trauma, congenital malformations, 5-minute Apgar score less than 7, prematurity, and gestational age at birth.

Overall, none of the systematic reviews examined found any evidence of adverse maternal or neonatal effects when using oral antihyperglycaemic therapy (glibenclamide, metformin or acarbose) compared with insulin. However, they stressed that primary studies had important quality problems (many studies with small sample sizes, many cohort studies rather than RCTs) and that some important outcomes were not assessed.

TABLE II Systematic review conclusions

| Study | Conclusions | Recommendations | Comments |
|------------------------------|---|--|---|
| Moretti 2008 ⁵⁴ | <p><i>Maternal outcomes:</i> no outcomes reported</p> <p><i>Neonatal outcomes:</i> meta-analysis does not suggest increased perinatal risks with glibenclamide compared with insulin</p> | <p><i>Research:</i> further evaluation needed</p> <p><i>Practice:</i> no practice recommendations given</p> | Most studies were non-randomised; in several studies treatment was only switched to insulin after glibenclamide failure |
| NICE 2008 ² | <p><i>General:</i> in women requiring hypoglycaemic therapy, between 79% and 96% of women will achieve BG targets on glibenclamide. The relative prevalence of maternal hypoglycaemia and LGA babies compared with insulin therapy differs between studies</p> | <p><i>Research:</i> no relevant research recommendations given</p> <p><i>Practice:</i> hypoglycaemic therapy should be considered for women with gestational diabetes if ultrasound investigation suggests incipient fetal macrosomia (abdominal circumference above the 70th percentile) at diagnosis</p> <p>Hypoglycaemic therapy for women with gestational diabetes [which may include regular insulin, rapid-acting insulin analogues (aspart and lispro) and/or hypoglycaemic agents (metformin and glibenclamide)] should be tailored to the glycaemic profile of, and acceptability to, the individual woman</p> | |
| Nicholson 2009 ⁵⁵ | <p><i>Maternal outcomes:</i> overall, adverse maternal outcomes were no more frequent with glibenclamide, acarbose or metformin than with insulin</p> <p><i>Neonatal outcomes:</i> overall, no more adverse neonatal outcomes were seen with glibenclamide, acarbose or metformin than with insulin</p> | <p><i>Research:</i> studies with sufficient power needed to detect meaningful differences in maternal and neonatal outcomes</p> <p>Definitions of maternal and neonatal outcomes need to be consistent across trials</p> <p>Studies designed to address glucose thresholds for medication use</p> <p><i>Practice:</i> glibenclamide and metformin appear to be effective alternatives to insulin</p> | Studies did not report some important outcomes such as perineal tears and operative vaginal delivery; no evidence for variation in maternal and neonatal outcomes on the basis of glucose level at initiation of antihyperglycaemic therapy; no standard definition of maternal hypoglycaemia; quality limitations of studies |

The reviews' conclusions are shown in *Table 11*. A full description of the reviews and their findings is given in Appendices 2 and 3.

Primary studies

Description of primary studies

The main characteristics of the included primary studies are shown in Appendix 4. Details regarding the participants and diagnostic criteria are shown in Appendix 5. Results of the quality assessment are shown in Appendix 6 for RCTs and in Appendix 7 for cohort studies. An abstract by Nasruddin (2009)⁹² appeared to be an extension of the study by Holt (2008)⁵² with 145 women in the glibenclamide and insulin groups rather than 89, but, as the results were no different from those in the original paper, this was largely ignored here.

Seven of the observational studies were prospective cohort studies and 11 were retrospective cohort studies. For two studies it was unclear. Nineteen studies included participants from the USA, and the remainder included participants from Australia, New Zealand, Brazil, Finland, India, Israel, South Africa and the UK. See Appendix 4 for details of characteristics of the primary studies.

Most of the studies did not report duration of follow-up and follow-up was presumed to last until collection of data related to delivery. Only one RCT⁸⁸ reported data for up to 6 – 8 weeks after delivery.

The studies included a total of 4425 participants, 2413 in studies comparing glibenclamide with insulin, 815 in studies of glibenclamide failure, and 1135 in trials comparing metformin and insulin. One trial⁶⁷ included 19 patients treated with acarbose and one cohort study⁷⁰ included 43 patients treated with a combination of glibenclamide and metformin. Individual comparison groups included between 7 and 385 patients, with only five studies (two RCTs and three cohort studies)^{68,74–76,88} including more than 100 patients per study group.

Most studies specified BG targets and used pharmacological therapy after failure of diet therapy (for details see Appendix 4 and Appendix 5). Glibenclamide was generally used in doses of up to a maximum of 20 mg/day, and metformin to a maximum of between 2000 and 2500 mg/day (where reported). BG targets differed somewhat between studies. Most studies specified criteria for failure of oral therapy (and consequent switching

to insulin therapy, see Appendix 4). Most studies focused on neonatal and obstetric outcomes. Specific maternal outcomes including glycaemic control following treatment, treatment satisfaction and maternal adverse effects were reported by only a few studies. Only two of the studies reported on post-partum glucose tolerance^{88,89} and none reported on maternal anxiety, depression or health status. Sixteen studies reported on the proportion of patients who failed oral therapy and were switched to insulin therapy. However, of these studies, only two reported whether patients in the insulin group had adequate glycaemic control (see Appendix 4).

Women in the trials had a mean age of between 25 and 35 years. Where reported, between 7.7% and 62% were nulliparous. Pre- (or early) pregnancy BMI was between 23 and 40 kg/m² with many trials including a large proportion of obese women (see Appendix 5), and two focusing on obese women.^{71,76} Ethnicity was only reported by a few studies. Between 14% and 83% of women had a diabetes family history (where reported). Mean gestational age at the start of oral therapy was between 18 and 33 weeks. Diagnostic criteria for commencement of pharmacological therapy varied somewhat between studies (see Appendix 5). In the study by Ramos (2007)⁶¹ there was some overlap in participants with the study by Jacobson (2005).⁷⁵ However, the study by Ramos (2007)⁶¹ included only women with more severe hyperglycaemia (≥ 11.1 mmol/l and FPG ≥ 5.8 mmol/l on the oral GCT). Where reported, women had baseline fasting blood glucose (FBG) values on the OGTT of between 5.2 and 6.6 mmol/l and 2-hour values of between 9.4 and 11.3 mmol/l.

The quality of the included studies was limited (see Appendices 6 and 7). Most of the studies were underpowered. None of the studies (RCTs or cohort studies) reported blinded outcome assessment. Of the seven RCTs, only two fulfilled more than half of the quality criteria specified and none fulfilled all of them. See Appendix 6 for details of the quality of the RCTs. Of the 20 cohort studies, seven fulfilled more than half of the quality criteria specified (see Appendix 7) and none fulfilled all of them.

Results of primary studies

An overview of the primary and secondary results is shown in Appendix 8.

The results are summarised in *Tables 12* and *13*.

TABLE 12 Summary of treatment effects for studies comparing glibenclamide versus insulin

| Outcome | Number of RCTs | Significance of effect | Comment | Number of observational studies (including abstracts) | Significance of effect | Comment |
|---|----------------|------------------------|--|---|------------------------|---|
| Maternal/obstetric: primary outcomes | | | | | | |
| Pre-eclampsia/hypertensive complications | 1 | NS | | 4 | NS | |
| Caesarean delivery | 3 | NS | | 6 | NS | Two abstracts alone significantly favoured glibenclamide – overall NS |
| Maternal FPG during pregnancy | 1 | NS | | 1 | Significant | Mean difference 0.41 (95% CI -0.58 to 0.24) mmol/l; $p < 0.00001$. Favours glibenclamide |
| Maternal 2-hour PG during pregnancy | 1 | NS | | 1 | NS | |
| Maternal mean BG during pregnancy | 1 | NS | | 1 | NS | |
| Maternal HbA _{1c} during pregnancy | 2 | NS | Significant heterogeneity; effects in opposite direction | | | |
| Maternal hypoglycaemia | 3 | Significant | Two of three RCTs had no events One RCT significantly favoured glibenclamide RR 0.10 (95% CI 0.04 to 0.27); $p < 0.00001$ | 2 | NS | Both studies significant but in opposite directions |
| Maternal/obstetric: secondary outcomes | | | | | | |
| Induction of labour | | | | 2 | NS | |
| Maternal weight gain | 2 | NS | | 2 | NS | |
| Post-partum glucose tolerance | | | | | | |
| Acceptability of treatment | | | | | | |
| Maternal anxiety | | | | | | |

TABLE 12 Summary of treatment effects for studies comparing glibenclamide versus insulin (continued)

| Outcome | Number of RCTs | Significance of effect | Comment | Number of observational studies (including abstracts) | Significance of effect | Comment |
|---|----------------|------------------------|--|---|------------------------|--|
| Depression | | | | | | |
| Health status | | | | | | |
| Child/neonatal: primary outcomes | | | | | | |
| Neonatal hypoglycaemia | 3 | Significant | RR 2.07 (95% CI 1.04 to 4.11); $p=0.04$. Favours insulin | 5 | NS | $p=0.07$, favours insulin |
| Birthweight | 4 | Significant | Mean difference 89.63 g (95% CI -1.48 to 180.75); $p=0.05$. Favours insulin | 5 | NS | |
| Macrosomia (birthweight ≥ 4000 g) | 2 | NS | | 6 | NS | One abstract found significant difference in favour of glibenclamide |
| LGA (>90th percentile) | 2 | NS | | 5 | NS | |
| Birth trauma (e.g. shoulder dystocia, bone fracture, nerve palsy) | 1 | NS | | 3 | NS | |
| Child/neonatal: secondary outcomes | | | | | | |
| Hyperbilirubinaemia rate | 1 | NS | | 2 | NS | |
| Need for phototherapy | 0 | | | 4 | NS | Significant heterogeneity. In two studies significantly higher rates in glibenclamide, one study in opposite direction |
| SGA (<10th percentile) | 1 | NS | | 3 | NS | |
| NICU admission | 1 | NS | | 6 | NS | One cohort study found significantly more NICU admission in the insulin group |

continued

TABLE 12 Summary of treatment effects for studies comparing glibenclamide versus insulin (continued)

| Outcome | Number of RCTs | Significance of effect | Comment | Number of observational studies (including abstracts) | Significance of effect | Comment |
|-----------------------------|----------------|------------------------|---|---|------------------------|---|
| Congenital malformations | 2 | NS | | 3 | NS | Heterogeneity – two in opposite directions |
| Respiratory distress | 1 | NS | | 4 | NS | |
| 5-minute Apgar score | 1 | Significant | Mean difference –0.40 (–0.76 to 0.04), $p=0.03$. Favours insulin | 4 | NS | |
| 1-minute Apgar score | 1 | NS | | 4 | NS | One obs study found a significantly higher 1-minute Apgar score favouring insulin group |
| Preterm delivery | 1 | NS | | 2 | NS | |
| Gestational age at delivery | 3 | NS | | 5 | NS | |

NS, not significant.
Values are mean \pm SD unless indicated otherwise.

TABLE 13 Summary of treatment effects for studies comparing metformin versus insulin

| Outcome | Number of RCTs | Significance of effect | Comment | Number of observational studies (including abstracts) | Significance of effect | Comment |
|---|----------------|------------------------|---------------------------|---|------------------------|---------|
| Maternal/obstetric: primary outcomes | | | | | | |
| Pre-eclampsia/hypertensive complications | 2 | NS | | 2 | NS | |
| Caesarean delivery | 3 | NS | Significant heterogeneity | 2 | NS | |
| Glycaemic control during pregnancy (FPG, 2 PG, mean BG, HbA _{1c}) | 2 | NS | | | | |
| Maternal hypoglycaemia | 1 | No events | | | | |
| Maternal/obstetric: secondary outcomes | | | | | | |
| Induction of labour | 3 | NS | | 1 | NS | |

TABLE 13 Summary of treatment effects for studies comparing metformin versus insulin (continued)

| Outcome | Number of RCTs | Significance of effect | Comment | Number of observational studies (including abstracts) | Significance of effect | Comment |
|---|----------------|------------------------|---|---|------------------------|--|
| Maternal weight gain | 1 | Significant | More weight gain (2 kg vs 0.4 kg, $p < 0.001$) in the insulin than in the metformin group; favours metformin | 2 | n.a. | One study significantly favoured metformin, one study showed no significant difference |
| Post-partum glucose tolerance | 1 | NS | | 1 | NS | |
| Acceptability of treatment | | | | | | |
| Maternal anxiety | | | | | | |
| Depression | | | | | | |
| Health status | | | | | | |
| Child/neonatal: primary outcomes | | | | | | |
| Neonatal hypoglycaemia | 2 | NS | | 2 | Significant | RR 0.60 (0.37 to 0.95) $p = 0.03$. Favours metformin |
| Birthweight | 3 | NS | | 2 | NS | |
| Macrosomia (birthweight ≥ 4000 g) | 2 | NS | | 2 | NS | |
| LGA (> 90 th percentile) | 1 | NS | | 1 | NS | |
| Perinatal mortality | 2 | NS | | 2 | NS | |
| Birth trauma (e.g. shoulder dystocia, bone fracture, nerve palsy) | 2 | NS | | 2 | NS | |
| Child/neonatal: secondary outcomes | | | | | | |
| Hyperbilirubinaemia rate | 2 | NS | | 2 | NS | |
| Need for phototherapy | 2 | NS | | 2 | NS | |
| SGA (< 10 th percentile) | 1 | NS | | 2 | NS | |
| NICU admission | 2 | NS | | 2 | NS | One study (published as abstract) found significantly in favour of metformin |
| Congenital malformations | 1 | NS | | 3 | NS | |

continued

TABLE 13 Summary of treatment effects for studies comparing metformin versus insulin (continued)

| Outcome | Number of RCTs | Significance of effect | Comment | Number of observational studies (including abstracts) | Significance of effect | Comment |
|-----------------------------|----------------|------------------------|--|---|------------------------|--|
| Respiratory distress | 2 | NS | | 1 | NS | |
| 5-minute Apgar score <7 | 1 | NS | | 1 | NS | |
| 1-minute Apgar score | | | | | | |
| Preterm delivery | 1 | Significant | Higher with metformin than with insulin (12.1% vs 7.6%, $p=0.04$). Favours insulin | 2 | NS | Direct of effect opposite to RCTs in both cohort studies |
| Gestational age at delivery | 3 | Significant | Mean difference of -0.21 weeks (95% CI -0.40 to -0.02) ($p=0.03$) lower gestational age with metformin. Favours insulin | 1 | NS | In opposite direction to RCTs |

n.a., not appropriate to combine studies; NS, not significant.
Values are mean \pm SD unless indicated otherwise.

Maternal/obstetric outcomes: primary outcomes

Pre-eclampsial/hypertensive complications

Glibenclamide versus insulin

One RCT by Langer (2005)⁶⁸ reported no difference in pre-eclampsia after treatment with glibenclamide versus insulin.

Four observational ones gave differing results (Figure 1). One cohort study (Jacobson 2005⁷⁵) reported significantly higher pre-eclampsia rates with glibenclamide than with insulin (12% vs 6%), but no differences were found in the other observational studies (Ramos 2007⁶¹ which provided data as in Figure 1, and Duncan 2005⁷¹ and Patterson 2008⁷⁷ which only reported no differences). Taking both RCTs and observational studies together, there were between 6% and 12% of women with pre-eclampsia (where reported).

Acarbose versus insulin

Pre-eclampsia rates were not reported for acarbose versus insulin.

Metformin versus insulin

Two RCTs (Hague 2003⁸⁵ and Rowan 2008⁸⁸) reported no difference in pre-eclampsia after treatment with metformin versus insulin (Figure 2).

Nor did two cohort studies (Tertii 2008⁵⁶ and Balani 2008⁸⁹) find any difference in pre-eclampsia rates between metformin and insulin.

Overall, there were between 5.5% and 19% of women with pre-eclampsia. Balani (2008),⁸⁹ Tertti (2008),⁵⁶ and Rowan (2008)⁸⁸ found no significant difference in pregnancy-induced hypertension rates between metformin and insulin groups.

Caesarean delivery

Glibenclamide versus insulin

Three RCTs reported no differences in caesarean delivery rates for women treated with

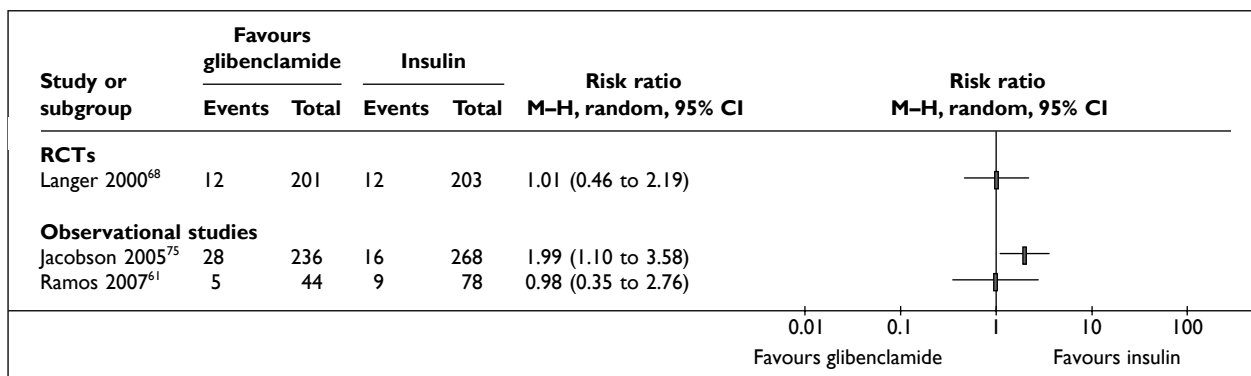


FIGURE 1 Pre-eclampsia: glibenclamide versus insulin.

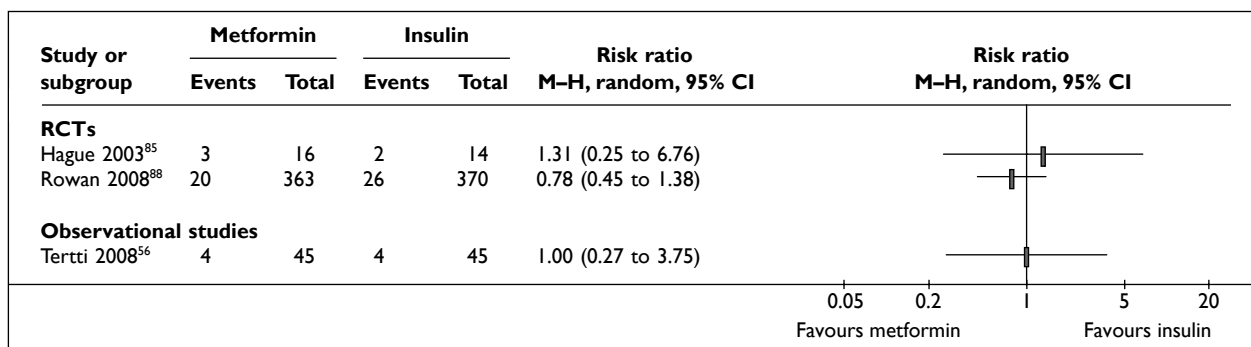


FIGURE 2 Pre-eclampsia: metformin versus insulin.

glibenclamide versus insulin (Figure 3). The RR was 0.91 (95% CI -0.71 to 1.16).

Five observational studies (Figure 3 and Patterson 2008⁷⁷) published as full papers reported no significant differences between treatment groups. However, Duncan (2005),⁷¹ published as an abstract, reported a significant difference in caesarean sections in favour of glibenclamide for non-morbidly obese women but not for morbidly obese women. The RR was 1.04 (95% CI 0.84 to 1.28) for cohort studies published in full, and 0.53 (95% CI 0.36 to 0.77, $p = 0.001$) for cohort studies published as abstracts. However, when combining the observational cohort studies published in full with those published as abstracts the RR was not significant, i.e. 0.82 (95% CI 0.59 to 1.14).

Overall, between 14% and 56% of women had caesarean deliveries.

Five per cent of women in the glibenclamide group and 6% of women in the insulin group had an operative vaginal delivery (no significant

difference); 7% of deliveries in the glibenclamide group and 9% in the insulin group were assisted vaginal deliveries.

Acarbose versus insulin

Bertini (2005)⁶⁷ did not report any significant difference in caesarean delivery rates between women receiving acarbose or insulin (53% and 44%), RR 1.18 (95% CI 0.65 to 2.16) (Figure 4).

Metformin versus insulin

Three RCTs (Hague 2003,⁸⁵ Moore 2007⁸⁶ and Rowan 2008⁸⁸) reported on caesarean delivery rates for women treated with metformin versus insulin (Figure 5). Significant heterogeneity was noted. However, the largest study (Rowan 2008⁸⁸) did not demonstrate any appreciable or significant difference between women treated with insulin and those treated with metformin. Between 21% and 63% of women had caesarean deliveries. The overall RR for the RCTs was 1.41 (95% CI 0.77 to 2.58) (but with significant heterogeneity). Rowan (2008)⁸⁸ reported that 15% of the metformin group

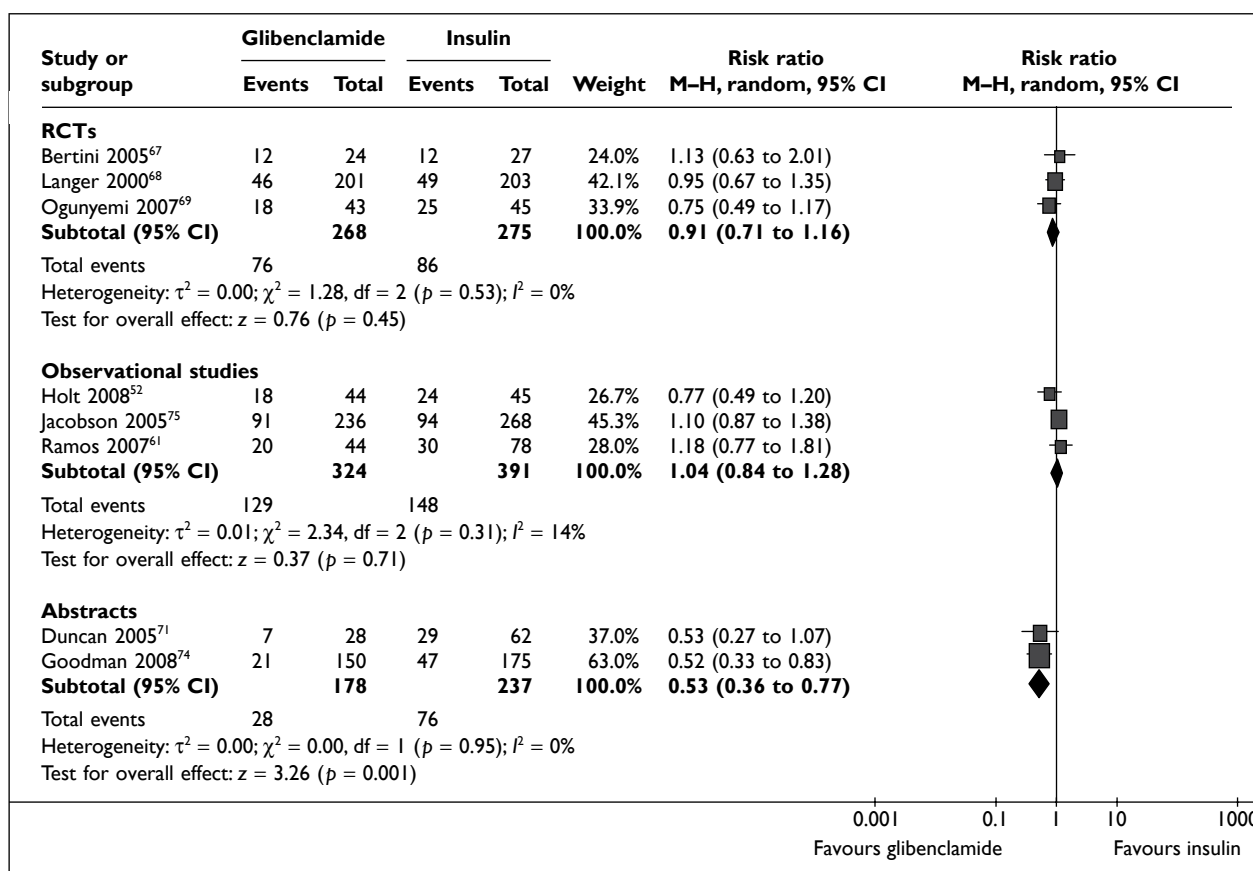


FIGURE 3 Caesarean delivery: glibenclamide versus insulin.

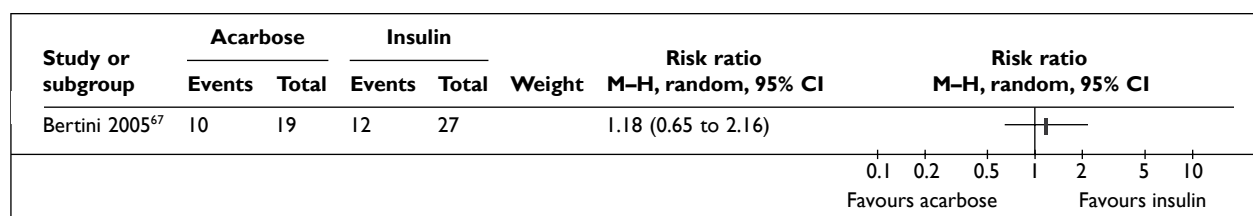


FIGURE 4 Caesarean delivery: acarbose versus insulin.

and 17% of the insulin group had an emergency caesarean delivery (no significant difference).

Two observational studies (Tertti 2008⁵⁶ and Balani 2008⁸⁹) reported no significant difference.

Glycaemic control during pregnancy

Glibenclamide versus insulin

For mean BG, 2-hour PPG and HbA_{1c}, none of the studies found a significant difference between the glibenclamide groups and the insulin groups.

With respect to FBG one cohort study found significantly lower values among women receiving glibenclamide compared with insulin (mean difference -0.41 mmol/l in the study by Jacobson 2005⁷⁵) (Figure 6). However, the RCT by Langer (2000)⁶⁸ did not find any significant difference among women receiving glibenclamide or insulin. FBG values in the different studies after treatment were between 5.01 and 5.44 mmol/l, 2-hour post-prandial values were between 5.16 and 6.59 mmol/l, mean BG values were between 5.78 and 5.83 mmol/l and HbA_{1c} was between 5.3% and 5.5%.

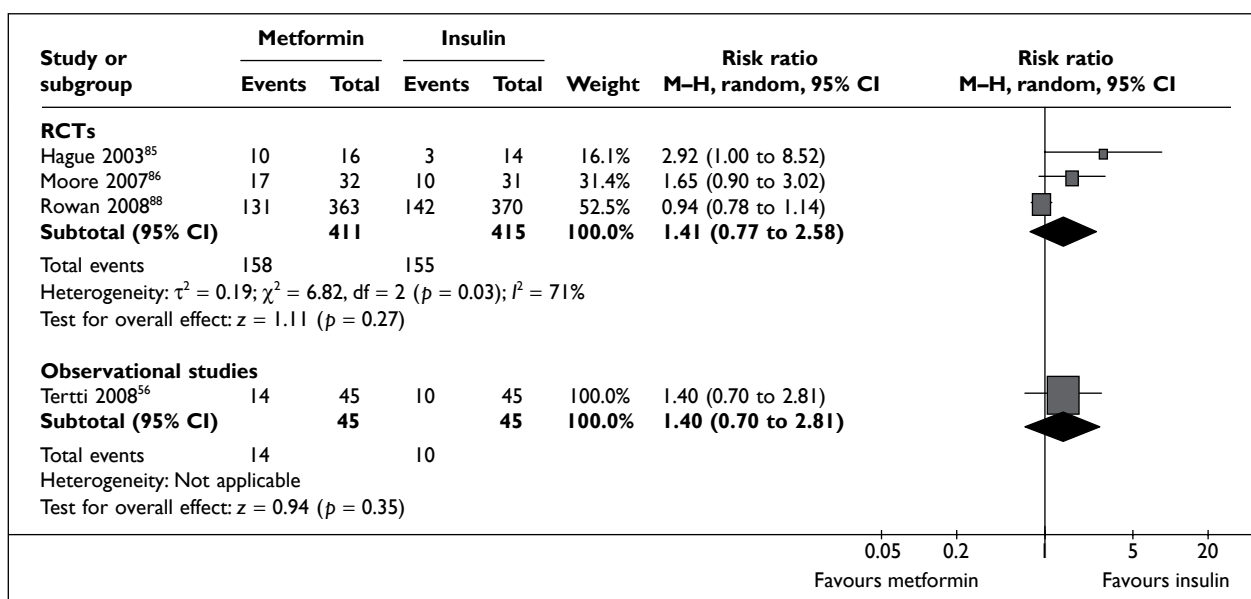


FIGURE 5 Caesarean delivery: metformin versus insulin.

Acarbose versus insulin

Maternal glycaemic control was not reported for acarbose versus insulin.

Metformin versus insulin

Two RCTs reported on maternal glycaemic control with metformin compared with insulin. Neither of the trials by Moore (2007)⁸⁶ or Rowan (2008)⁸⁸ found any significant difference in maternal FBG between metformin and insulin (FBG values between 5.09 and 5.37 mmol/l).

There was no significant difference in 2-hour post-prandial values in Moore (2007).⁸⁶ However, Rowan (2008)⁸⁸ found significantly lower 2-hour postprandial glucose values in the metformin group 1 week after randomisation and overall (mean difference -0.20 mmol/l for both measurements, $p < 0.01$) but not during the last 2 weeks before delivery. Mean 2-hour post-prandial values were between 5.9 and 6.69 mmol/l in the two studies. Rowan (2008)⁸⁸ reported no significant difference between treatment groups with respect to HbA_{1c} values.

Hypoglycaemia

Glibenclamide versus insulin

Three RCTs reported on maternal hypoglycaemia (Figure 7).

The trials by Anjalakshi (2007)⁶⁶ and Bertini (2005)⁶⁷ reported no maternal hypoglycaemia in either the glibenclamide or the insulin groups

(hypoglycaemia requiring hospital admission in Bertini 2005;⁶⁷ not defined in Anjalakshi 2007⁶⁶). However, Langer (2000)⁶⁸ found significantly less hypoglycaemia (BG < 2.2 mmol/l) in the glibenclamide group than in the insulin group [20% vs 2%, RR 0.10 (95% CI 0.04 to 0.27), $p = 0.03$]; none of the women reported severe symptoms.

Two observational studies reported different outcomes. Jacobson (2005)⁷⁵ found slightly but significantly more hypoglycaemia (values < 3.3 mmol/l) in the glibenclamide group than in the insulin group [0.20% vs 0.08%, RR 2.40 (95% CI 1.41 to 4.07), $p < 0.001$]. Yogev (2004),⁷⁸ however, found significantly less asymptomatic hypoglycaemia (BG ≤ 4.0 mmol/l) with glibenclamide than with insulin (in 28% vs 63% of women with 242 vs 46 episodes, $p = 0.04$); no symptomatic hypoglycaemic episodes were reported.

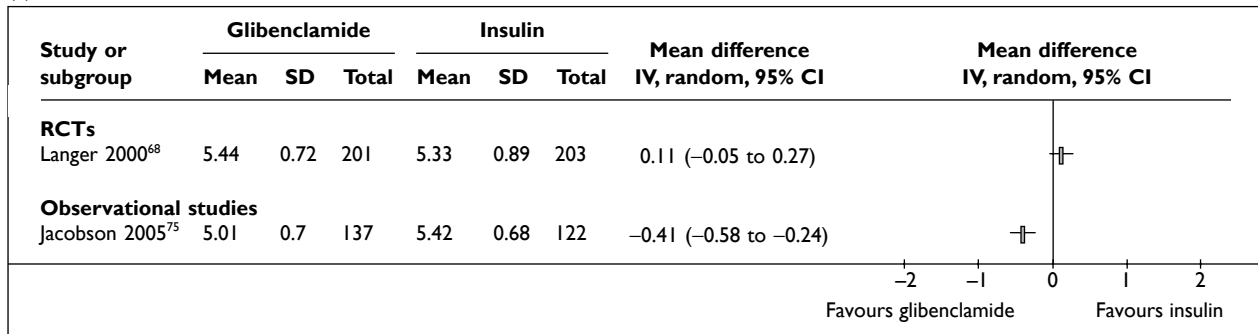
Acarbose versus insulin

Bertini (2005)⁶⁷ found no maternal hypoglycaemia requiring hospitalisation for acarbose versus insulin.

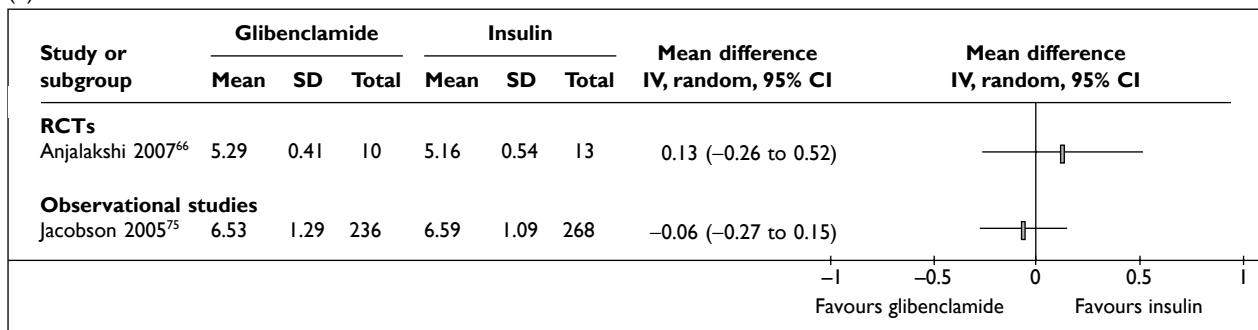
Metformin versus insulin

Only the RCT by Moore (2007)⁸⁶ reported maternal hypoglycaemia after treatment with metformin versus insulin. No cases of maternal hypoglycaemia were seen (hypoglycaemia not clearly defined).

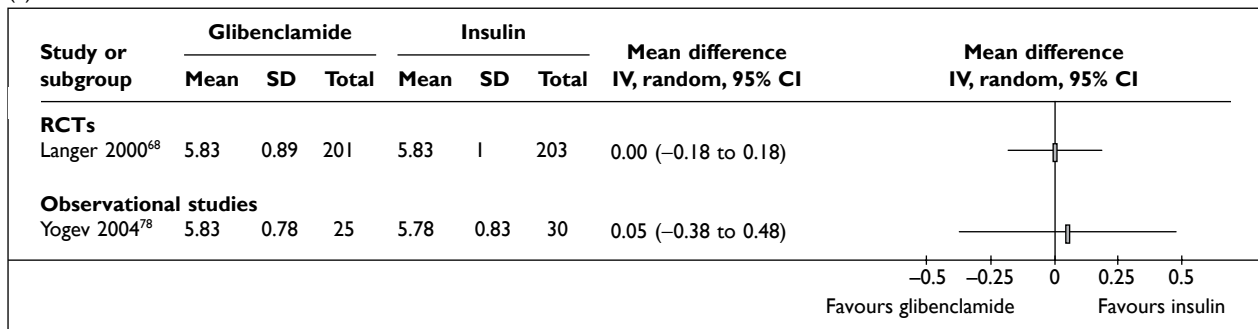
(a)



(b)



(c)



(d)

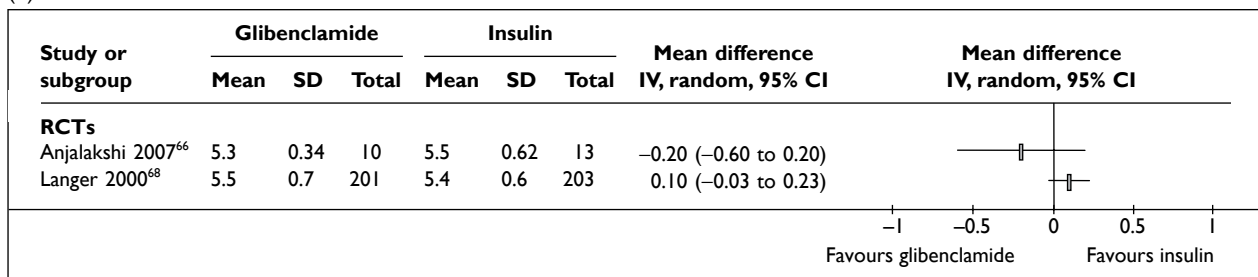


FIGURE 6 Maternal glycaemic control: glibenclamide versus insulin: (a) maternal FPG (mmol/l); (b) maternal 2-hour PG (mmol/l); (c) maternal mean BG; (d) maternal HbA_{1c} (%).

Neonatal/child outcomes: primary outcomes

Hypoglycaemia

Glibenclamide versus insulin

Three RCTs (as shown in *Figure 8*) examined

neonatal hypoglycaemia (see Appendix 4 for the various definitions). Bertini (2005)⁶⁷ found significantly more neonatal hypoglycaemia with glibenclamide than with insulin (33–34% with glibenclamide vs 4–14% with insulin).

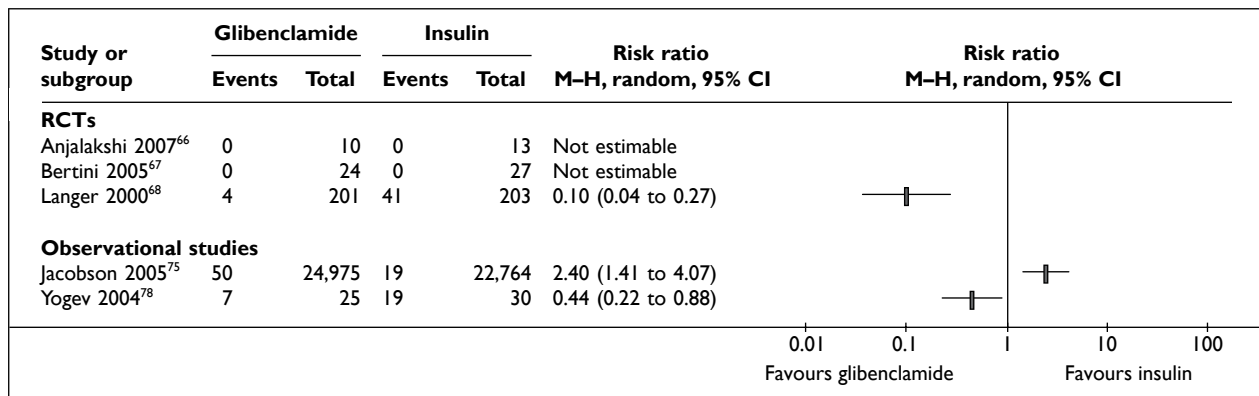


FIGURE 7 Maternal hypoglycaemia: glibenclamide versus insulin.

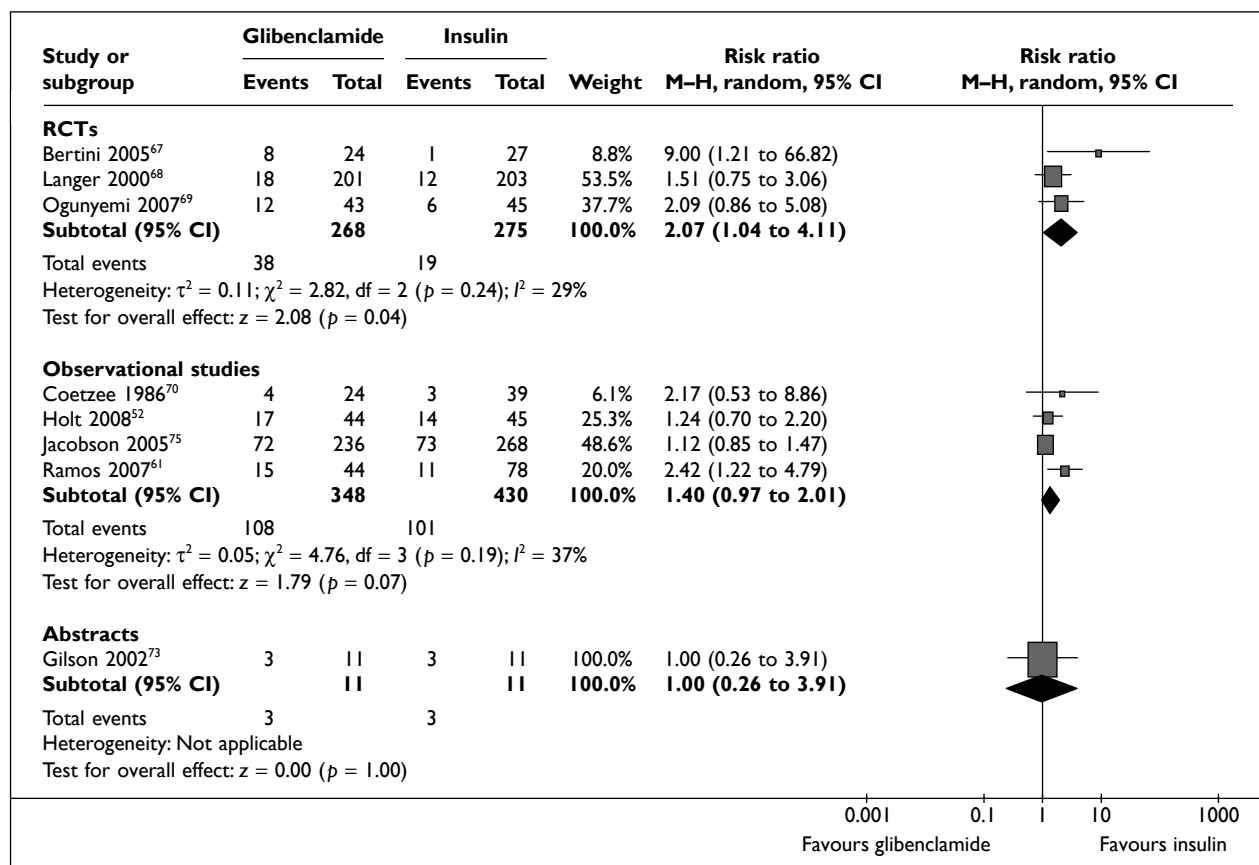


FIGURE 8 Neonatal hypoglycaemia: glibenclamide versus insulin.

Ogunyemi (2007)⁶⁹ reported significantly lower neonatal lowest glucose levels with glibenclamide than with insulin (2.65 ± 1.0 mmol/l vs 3.20 ± 1.0 mmol/l, $p = 0.028$).

In the RCTs overall, there was significantly more neonatal hypoglycaemia (BG < 2.2 mmol/l) with glibenclamide than with insulin [14% vs 7%, RR

2.07 (95% CI 1.04 to 4.11), $p = 0.04$] (no significant heterogeneity).

Five observational studies also reported neonatal hypoglycaemia. Significance was not quite reached when summarising only the cohort studies (for BG between < 1.4 and 2.6 mmol/l). Rates of neonatal

hypoglycaemia over all the studies ranged between 8% and 39%.

Acarbose versus insulin

Bertini (2005)⁶⁷ reported no significant difference in neonatal hypoglycaemia between acarbose and insulin (one case in each group) (Figure 9).

Metformin versus insulin

Two RCTs studies reported neonatal hypoglycaemia (with metformin versus insulin) (Figure 10). Neither found a significant difference in neonatal hypoglycaemia (below 2.2–2.6 mmol/l) between metformin and insulin. However, Rowan (2008)⁸⁸ found significantly higher rates of severe neonatal hypoglycaemia (BG < 1.6 mmol/l) with insulin than with metformin (8.1% vs 3.3%, *p* = 0.008).

One of two cohort studies, Terti (2008),⁵⁶ found significantly higher rates of hypoglycaemia (BG < 2.6 mmol/l) with insulin than metformin (58% vs 33%, *p* = 0.03). Overall values for the two cohort studies were slightly in favour of metformin [RR 0.60 (95% CI 0.38 to 0.95), *p* = 0.03].

Birthweight

Glibenclamide versus insulin

Four RCTs (including Goodman 2008,⁷⁴ an abstract without numeric data) examined birthweight after treatment with glibenclamide or insulin (Figure 11).

Neither the RCTs nor the cohort studies found any significant difference between the groups although the meta-analysis of RCT data demonstrated a borderline increased risk of higher birthweight among infants born to mothers that had received glibenclamide. The WMD was 89.63 g (95% CI -1.48 to 180.75).

Five cohort studies (including one, Goodman 2008⁷⁴ which gave no numerical data) reported birthweight. The WMD was -45.49 g (95% CI -218.36 to 127.37) for observational studies, and -27.6 g (95% CI -115.49 to 60.29) for abstracts (no significant heterogeneity). Goodman (2008)⁷⁴ reported no difference.

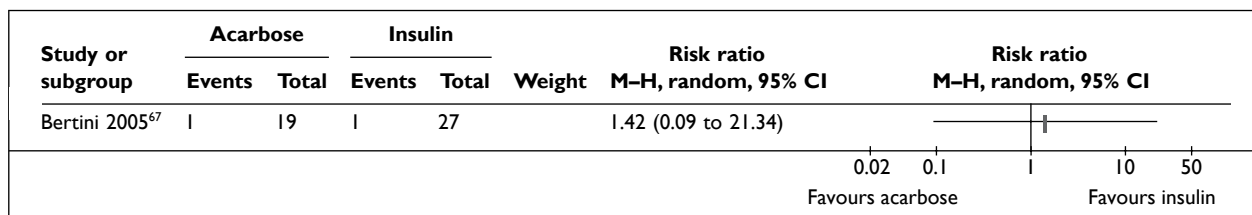


FIGURE 9 Neonatal hypoglycaemia: acarbose versus insulin.

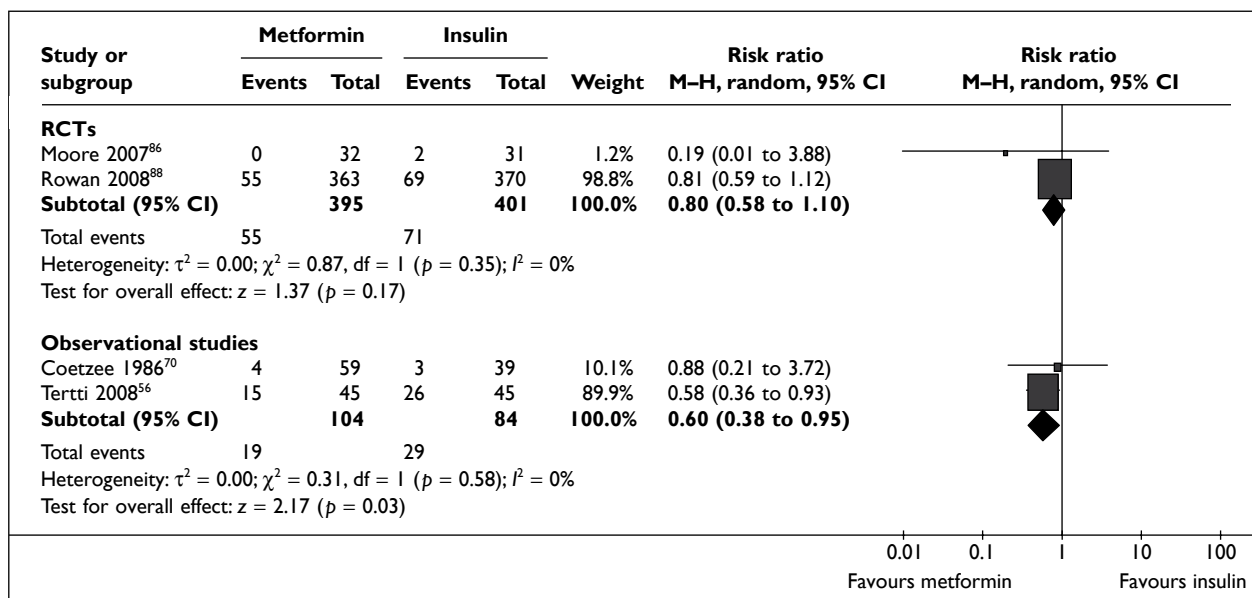


FIGURE 10 Neonatal hypoglycaemia: metformin versus insulin.

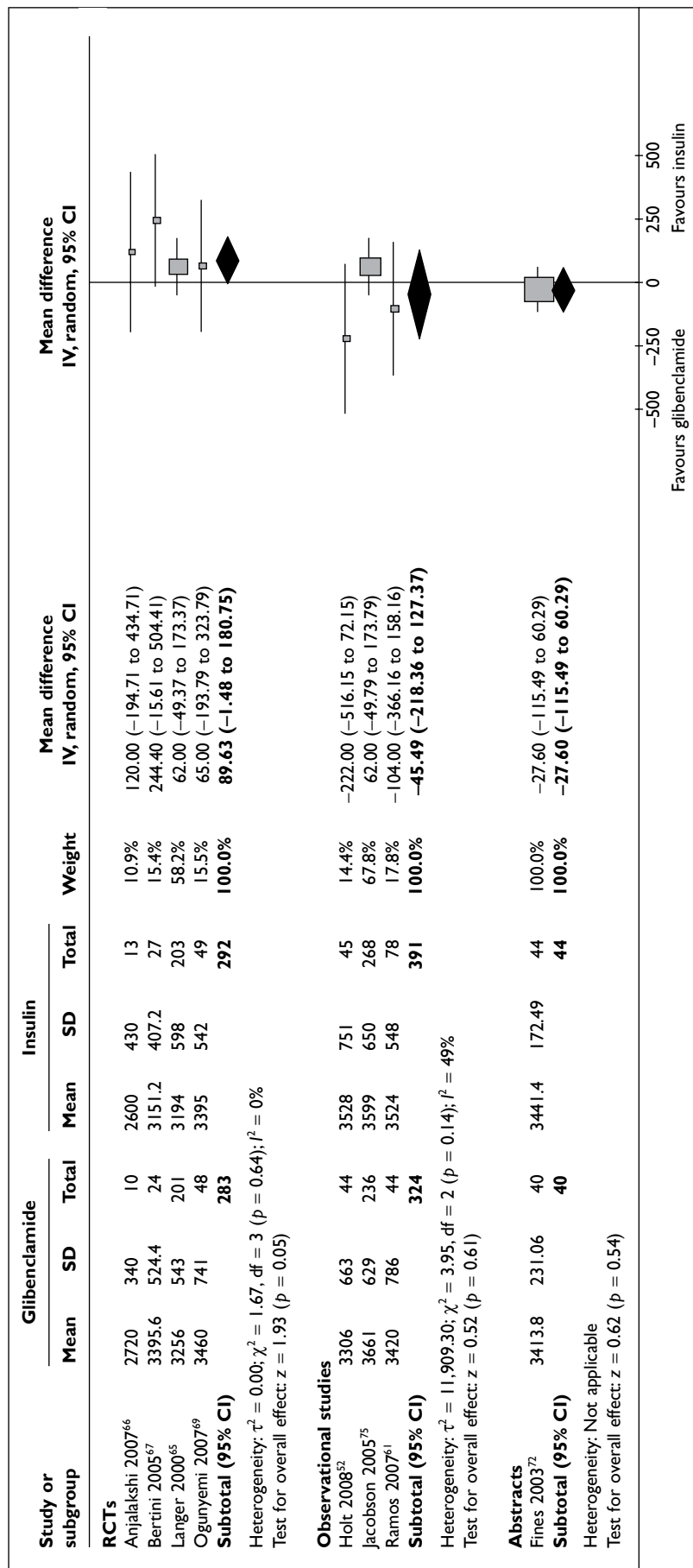


FIGURE 11 Birthweight: glibenclamide versus insulin.

| Study or subgroup | Oral agent | | | Insulin | | | Weight | Mean difference IV, random, 95% CI | Mean difference IV, random, 95% CI |
|----------------------------|------------|-------|-------|---------|-------|-------|--------|------------------------------------|------------------------------------|
| | Mean | SD | Total | Mean | SD | Total | | | |
| Bertini 2005 ⁸⁷ | 3242.6 | 400.6 | 19 | 3151.2 | 407.2 | 27 | 91.40 | (-145.32 to 328.12) | |
| | | | | | | | | | |

FIGURE 12 Birthweight: acarbose versus insulin.

| Study or subgroup | Metformin | | | Insulin | | | Weight | Mean difference IV, random, 95% CI | Mean difference IV, random, 95% CI |
|---|-----------|-------|------------|---------|-------|------------|---------------|------------------------------------|------------------------------------|
| | Mean | SD | Total | Mean | SD | Total | | | |
| RCTs | | | | | | | | | |
| Hague 2003 ⁸⁵ | 3560 | 500 | 16 | 3450 | 510 | 14 | 4.7% | 110.00 | (-252.48 to 472.48) |
| Moore 2007 ⁸⁶ | 3451.8 | 727.5 | 32 | 3500.2 | 700.5 | 31 | 5.0% | -48.40 | (-401.02 to 304.22) |
| Rowan 2008 ⁸⁸ | 3372 | 572 | 363 | 3413 | 569 | 370 | 90.3% | -41.00 | (-123.61 to 41.61) |
| Subtotal (95% CI) | | | 411 | | | 415 | 100.0% | -34.28 | (-112.80 to 44.24) |
| Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.64$, $df = 2$ ($p = 0.73$); $I^2 = 0\%$ Test for overall effect: $z = 0.86$ ($p = 0.39$) | | | | | | | | | |
| Observational studies | | | | | | | | | |
| Tertti 2008 ⁸⁶ | 3761 | 598 | 45 | 3759 | 642 | 45 | 100.0% | 2.00 | (-254.34 to 258.34) |
| Subtotal (95% CI) | | | 45 | | | 45 | 100.0% | 2.00 | (-254.34 to 258.34) |
| Heterogeneity: Not applicable Test for overall effect: $z = 0.02$ ($p = 0.99$) | | | | | | | | | |
| | | | | | | | | | |

FIGURE 13 Birthweight: metformin versus insulin.

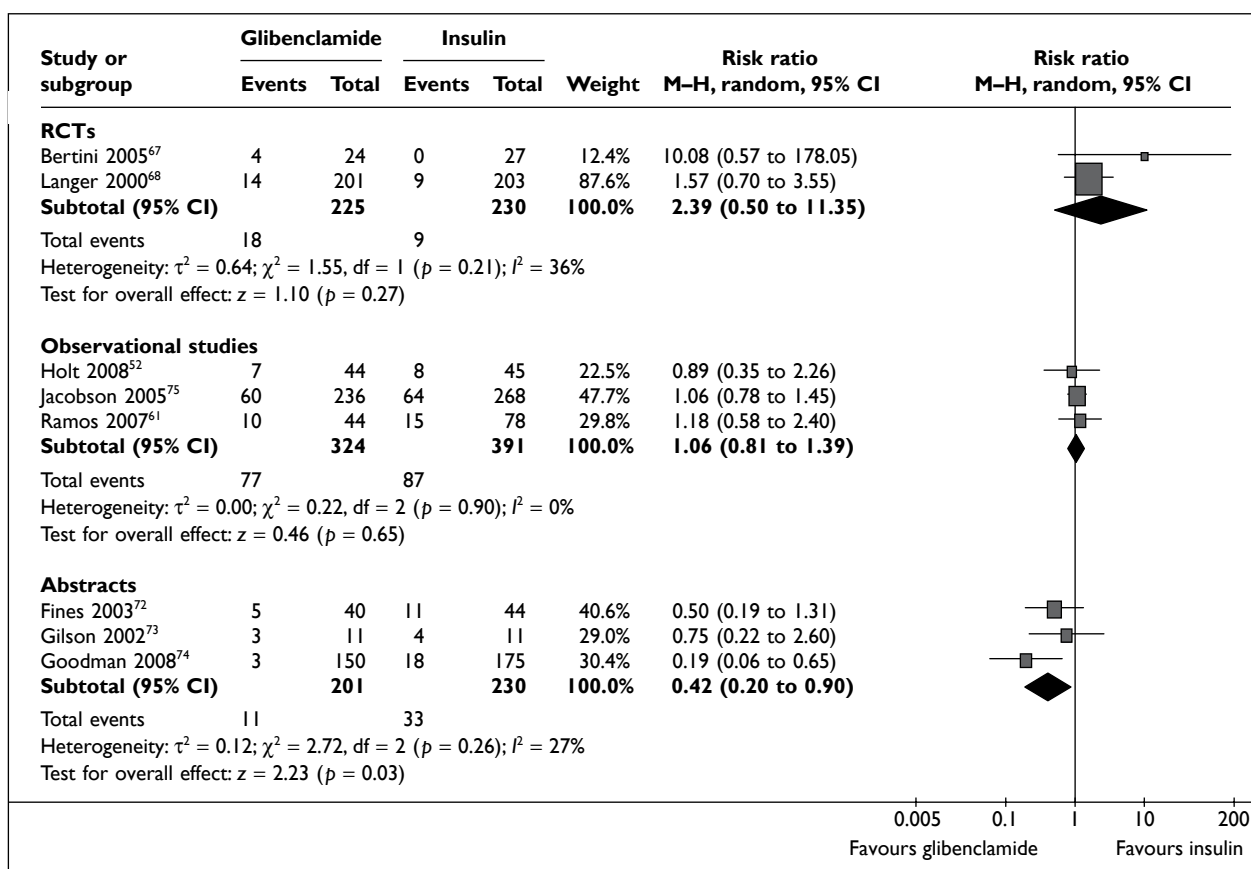


FIGURE 14 *Macrosomia: glibenclamide versus insulin.*

Acarbose versus insulin

No difference in birthweight was seen in the trial by Bertini (2005)⁶⁷ for after acarbose and insulin treatment (Figure 12). Mean birthweight was between 3151 and 3243 g.

Metformin versus insulin

Three RCTs examined birthweight after treatment with metformin or insulin (see Figure 13 and Balani 2008⁸⁹). Neither the RCTs nor the cohort studies found any significant difference between the groups. The WMD was -34.28 g (95% CI -112.80 to 44.24) for the RCTs.

The study by Rowan (2008)⁸⁸ also reported a range of other measurements of infant size and found no significant differences between metformin and insulin groups.

There were two cohort studies. Tertii (2008)⁵⁶ found no difference: -2.00 g (95% CI -254.34 to 258.34) for the observational study. Balani (2008)⁸⁹ reported no significant difference in an abstract without numerical data.

Macrosomia (birthweight ≥ 4000 g)

Glibenclamide versus insulin

Two RCTs and six cohort studies examined the effect of glibenclamide versus insulin on macrosomia rates (Figure 14).

Only the study by Goodman (2008),⁷⁴ published as an abstract, and using a 4500 g definition, found significantly more neonates weighing more than 4500 g in the insulin than in the glibenclamide group (2% vs 10.3%, $p = 0.004$). None of the other studies found a significant difference between the treatment groups. The RR was 2.39 (95% CI 0.50 to 11.35) for RCTs, 1.06 (95% CI 0.81 to 1.39) for observational studies, and 0.42 (95% CI 0.20 to 0.90, $p = 0.03$) for abstracts. Overall, macrosomia was observed in between 0% and 36% of neonates. Other studies: Langer (2006)⁷⁶ and Patterson (2008)⁷⁷ found no difference in macrosomia. Duncan (2005)⁷¹ reported more in the insulin group – about 23% versus none at all in the glibenclamide group.

Acarbose versus insulin

No macrosomia was seen in the trial by Bertini (2005)⁶⁷ when comparing acarbose with insulin.

Metformin versus insulin

Two RCTs examined the effect of metformin versus insulin on macrosomia rates (Figure 15). Neither found a significant difference between the treatment groups. Overall, macrosomia was observed in between 9% and 22% of neonates.

Two cohort studies, Tertii (2008)⁵⁶ and Balani (2008),⁸⁹ also found no difference.

A further observational study was identified that compared oral agents with insulin. It was published only as an abstract with sparse data, but the number of patients was large, and we report it for completeness. Cheng (2006)⁹⁴ reported on 11,463 women diagnosed with gestational diabetes and enrolled in the California Diabetes and Pregnancy Program in a retrospective cohort

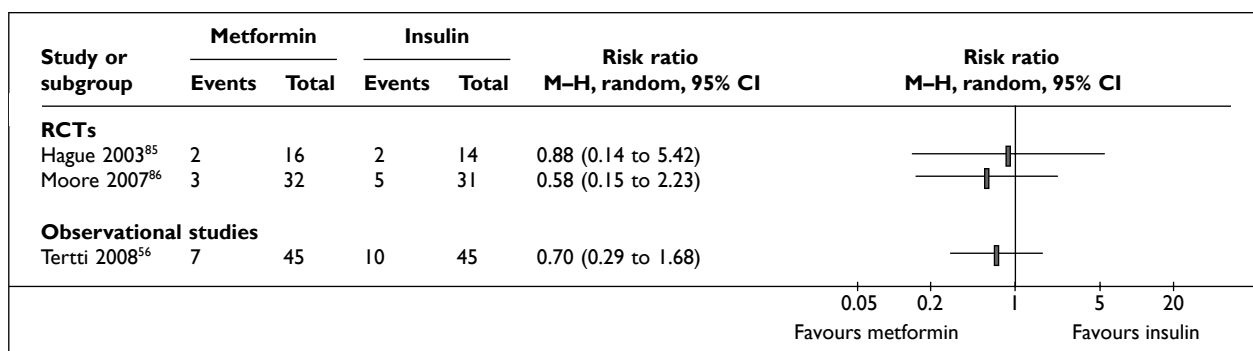


FIGURE 15 Macrosomia: metformin versus insulin.

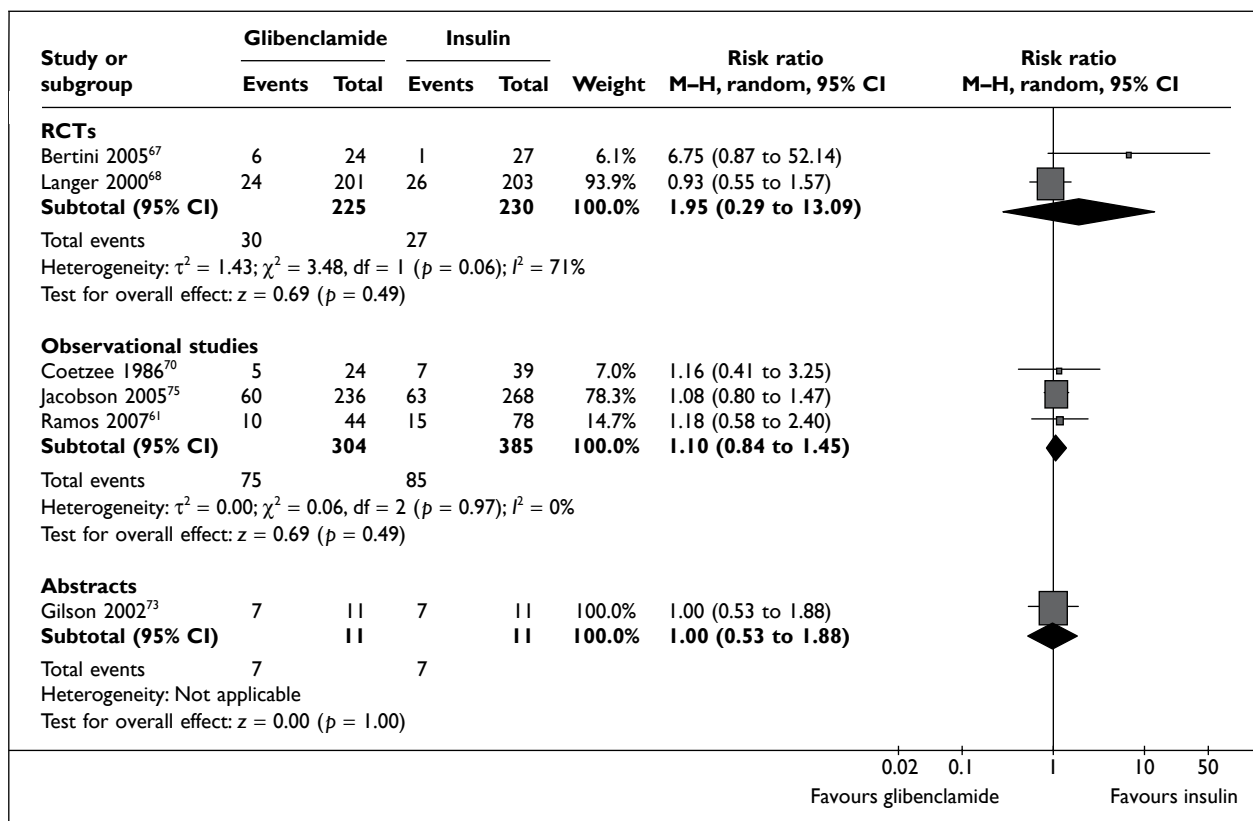


FIGURE 16 LGA: glibenclamide versus insulin.

study. Of these women, 18.6% were treated with oral agents and 81.4% were treated with insulin. After controlling for potential confounders (unspecified), significantly more macrosomia (birthweight > 4000 g, OR 1.28, 95% CI 1.01 to 1.63) was observed in the oral therapy group. Data on glycaemic control were not provided.

Large for gestational age (>90th percentile)

Glibenclamide versus insulin

Two RCTs (one the small Bertini⁶⁷ study; the other the large Langer⁷⁶ one) examined the effect of glibenclamide versus insulin on rates of LGA babies (Figure 16). The RR was 1.95 (95% CI 0.29 to 13.09).

Five cohort studies reported on LGA. None of the studies found a significant difference between the treatment groups, with RR 1.10 (95% CI 0.84 to 1.45) for observational studies, and 1.00 (95% CI 0.53 to 1.88) for the single abstract. Langer (2006)⁷⁶ reported no difference.

Acarbose versus insulin

No significant difference in rates of LGA neonates was seen in the trial by Bertini (2005)⁶⁷ when comparing acarbose with insulin (11% with acarbose and 4% with insulin, see Figure 17).

Metformin versus insulin

One RCT and one cohort study examined the effect of metformin versus insulin on rates of LGA neonates (Figure 18). Neither of the studies found a significant difference between the treatment groups. Between 15% and 19% of neonates were LGA.

Perinatal mortality

Most studies were underpowered for providing a reliable estimate of perinatal mortality, with almost all reporting no or one perinatal death. Given the small number of studies, meta-analysis cannot be any more helpful. Only the RCT by Langer (2000)⁶⁸ reported two perinatal deaths per comparison group (Figures 19 and 20). Bertini (2005)⁶⁷ found no perinatal mortality when comparing acarbose with insulin groups. There was no obvious difference between comparison groups.

Birth trauma (e.g. shoulder dystocia, bone fracture, nerve palsy)

Glibenclamide versus insulin

The RCT by Bertini (2005)⁶⁷ observed no birth trauma in either group.

Neither of the observational studies by Jacobson (2005)⁷⁵ and Ramos (2007)⁶¹ found a significant difference in birth trauma between groups. One cohort study published as an abstract (Gilson 2002⁷³) reported no difference in shoulder dystocia

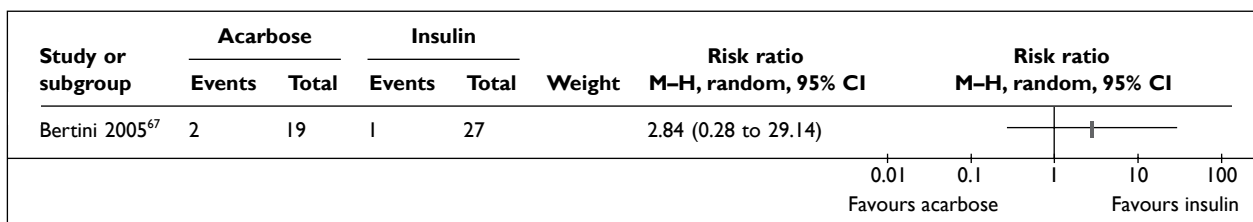


FIGURE 17 LGA: acarbose versus insulin.

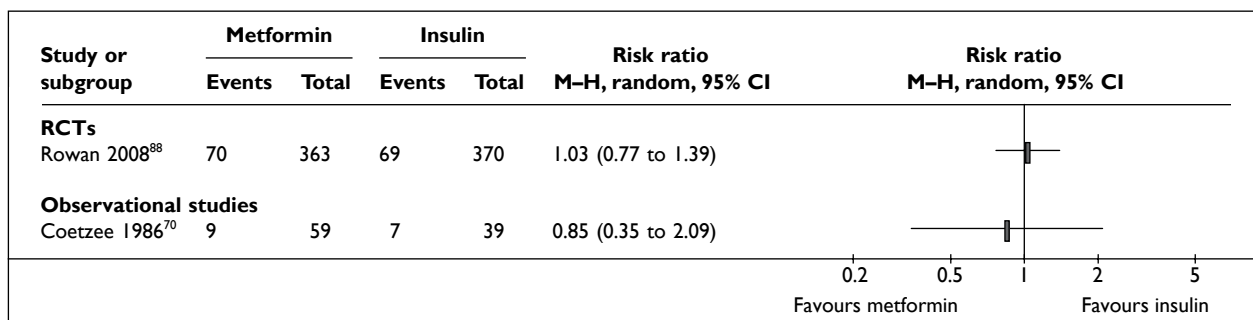


FIGURE 18 LGA: metformin versus insulin.

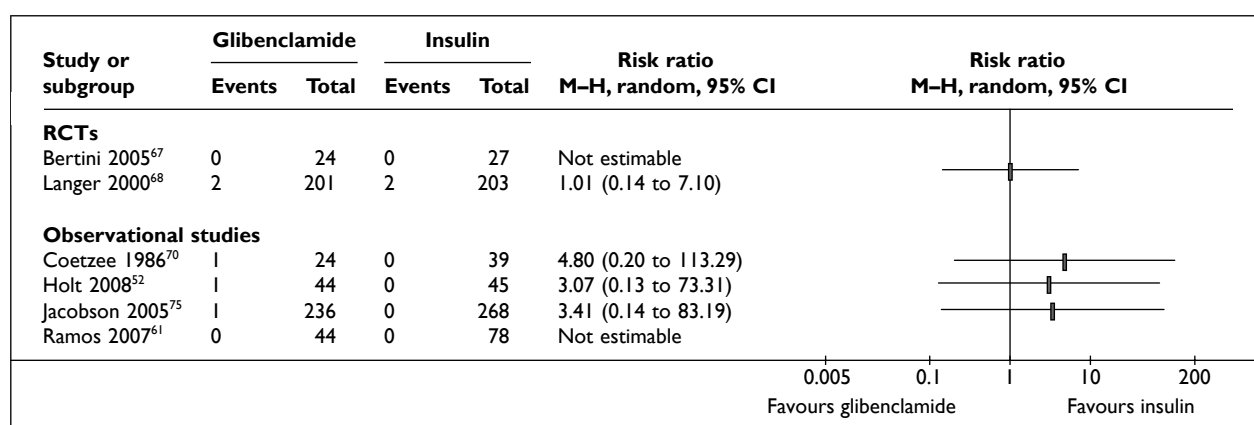


FIGURE 19 Perinatal mortality: glibenclamide versus insulin.

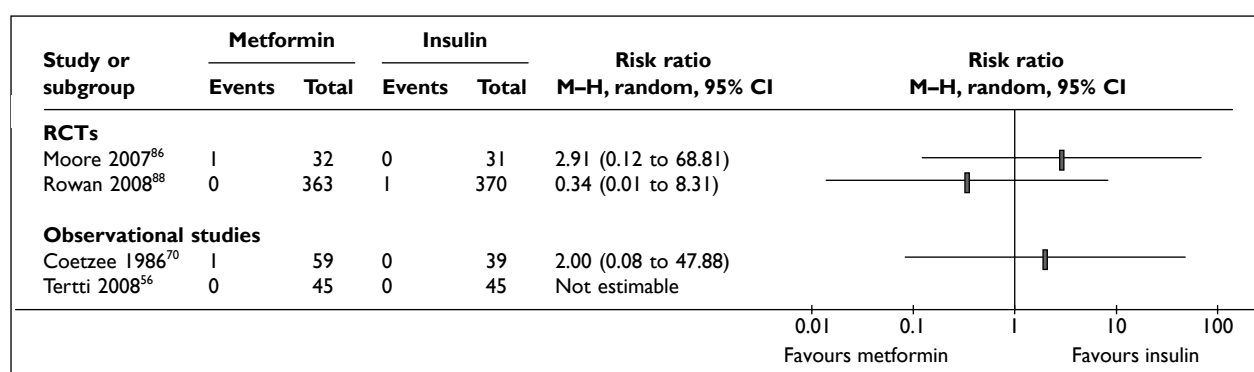


FIGURE 20 Perinatal mortality: metformin versus insulin.

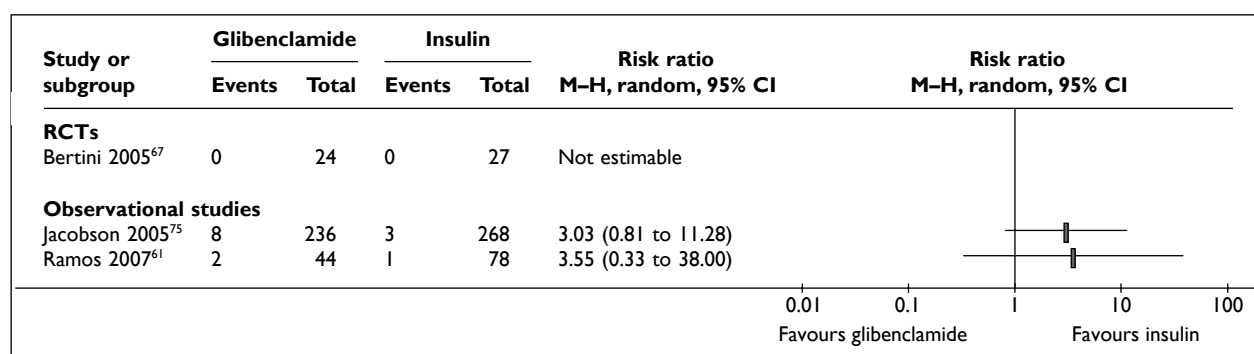


FIGURE 21 Birth trauma/shoulder dystocia: glibenclamide versus insulin.

between the glibenclamide and the insulin groups (Figure 21).

Acarbose versus insulin

Bertini (2005)⁶⁷ observed no birth trauma when comparing acarbose with insulin groups.

Metformin versus insulin

One RCT (Rowan 2008⁸⁸) reported on birth trauma after treatment with metformin or insulin (Figure 22). No significant difference in birth trauma rates was observed between the comparison groups.

Nor did the one cohort study (Tertii 2008⁵⁶) find any difference.

Two RCTs reported no significant difference in shoulder dystocia between the metformin and the insulin groups. Overall, there were between 0% and 3% of shoulder dystocias in the different studies.

Secondary outcomes

Information regarding the secondary outcomes (see Review of evidence on oral drugs, Inclusion criteria) are reported briefly here. A more detailed version is available on request.

Maternal/obstetric outcomes: secondary outcomes

Induction of labour

Glibenclamide versus insulin

Two cohort studies (Holt 2008⁵² and Duncan 2005⁷¹) reported on rates of induction of labour for glibenclamide versus insulin, with only Holt (2008)⁵² providing numerical data. There was no significant difference in induction of labour between the groups.

Metformin versus insulin

Three RCTs (Hague 2003,⁸⁵ Moore 2007,⁵³ Rowan 2008⁸⁸) found no significant difference between the treatment groups.

Maternal weight gain

A few studies reported maternal weight gain.

Glibenclamide versus insulin

Two RCTs reported no difference in maternal weight gain for women treated with glibenclamide versus insulin (Figure 23).

One of the two observational studies (Jacobson 2005⁷⁵) reported significantly more weight gain with glibenclamide than with insulin [mean difference 1.15 kg (95% CI 0.14 to 2.16)] $p = 0.03$. The other (Ramos 2007⁶¹) showed no difference.

Acarbose versus insulin

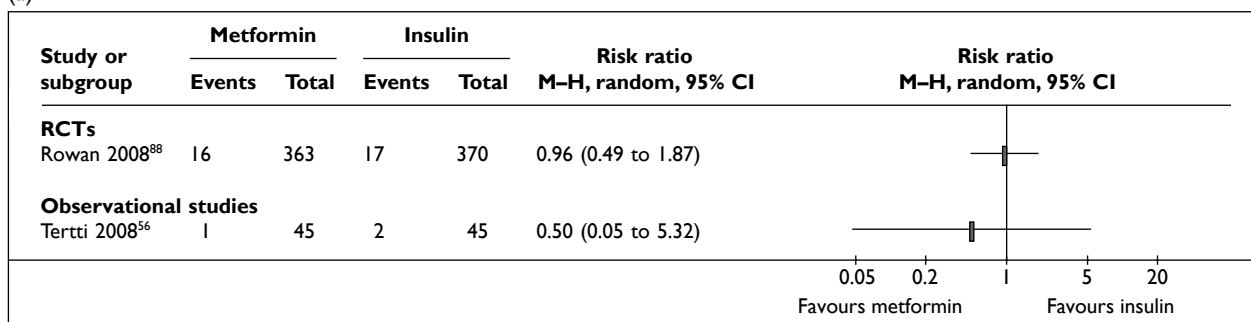
Bertini (2005)⁶⁷ reported no significant difference in maternal weight gain during pregnancy for acarbose versus insulin.

Metformin versus insulin

One RCT, Rowan (2008),⁸⁸ reported significantly more weight gain from enrolment to 36–37 weeks of gestation in the insulin group than in the metformin group [i.e. 2 kg (SD 3.3) vs 0.4 kg (SD 2.9), $p < 0.001$].

Similarly, one of the two observational studies, Balani (2008),⁸⁹ reported significantly more weight gain from enrolment until delivery in the insulin than in the metformin group (1.4 kg vs 0.3 kg, $p < 0.01$). The second observational study, Tertti (2008),⁵⁶ reported no significant difference in weight gain after the diagnosis of GDM of women receiving metformin or insulin, i.e. 3.0 (SD 3.6) versus 3.5 (SD 5.2) respectively. The mean number of gestational weeks at diagnosis was 24.5 weeks.

(a)



(b)

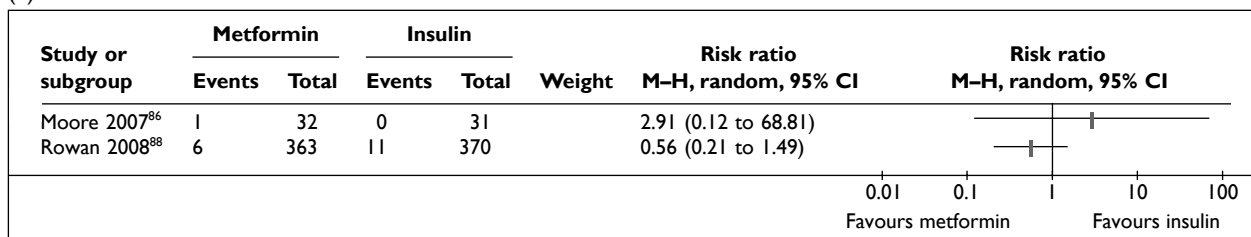


FIGURE 22 (a) Birth trauma; (b) shoulder dystocia: metformin versus insulin.

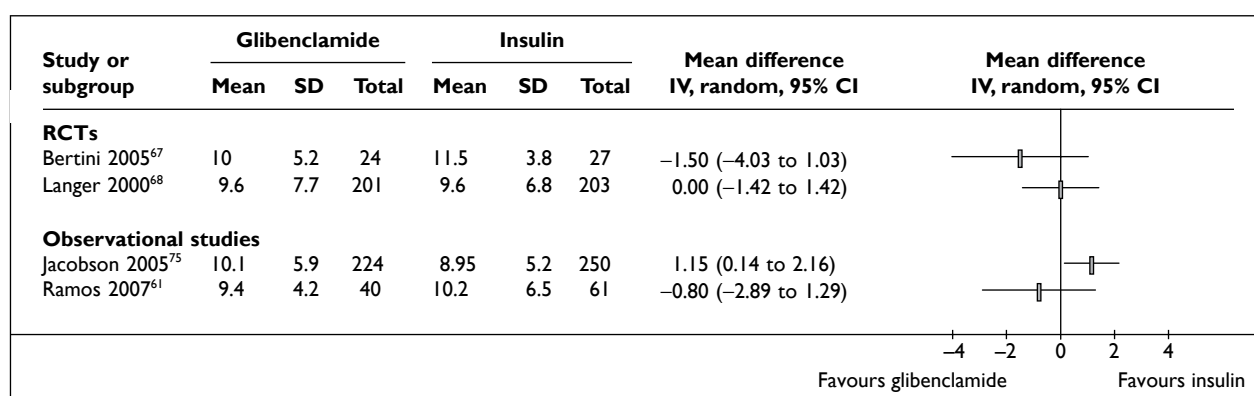


FIGURE 23 Maternal weight gain: glibenclamide versus insulin.

Post-partum glucose tolerance

Metformin versus insulin

One trial (Rowan 2008⁸⁸) of metformin versus insulin reported on post-partum glucose tolerance. A 75-mg OGTT was carried out at between 6 and 8 weeks post partum. There was no significant difference in any measures between the metformin and the insulin groups.

An observational study, Balani (2008),⁸⁹ found no significant difference between metformin and insulin groups in abnormalities in the post-natal glucose tolerance test.

Acceptability of treatment

Only three studies (Chmait 2004,⁷⁹ Holt 2008⁵² and Rowan 2008⁸⁸) gave some data on patient preference. None of the studies provided a detailed analysis of maternal adverse events considered to be treatment-related but five studies (Holt 2008,⁵² Jacobson 2005,⁷⁵ Kahn 2006,⁶³ Rochon 2006,⁸³ Rowan 2008⁸⁸) gave information on discontinuation/change of oral treatment because of adverse events. Details are shown in *Table 14*.

None of the studies reported data on the maternal outcomes of anxiety, depression or health status.

Child/neonatal outcomes: secondary outcomes

Hyperbilirubinaemia/need for phototherapy

Glibenclamide versus insulin

Two cohort studies (Jacobson 2005⁷⁵ and Ramos 2007⁶¹) and one RCT (Langer 2000⁶⁸) examined the rate of hyperbilirubinaemia in general.

As shown in *Figure 24*, none of the studies showed any significant difference between the glibenclamide and the insulin groups with respect to hyperbilirubinaemia.

Four cohort studies (Coetzee 1986,⁷⁰ Holt 2008,⁵² Jacobson 2005⁷⁵ and Ramos 2007⁶¹) examined the rates of hyperbilirubinaemia requiring phototherapy for glibenclamide versus insulin (see *Figure 24*). Two (Holt 2008⁵² and Jacobson 2005⁷⁵) showed significantly higher rates among infants born to mothers who received glibenclamide rather than insulin. When all four observational studies reporting this outcome were analysed together, there was no significant difference between the treatment groups. However, there was significant heterogeneity as a consequence of one study (Coetzee 1986⁷⁰) reporting in the opposite direction to the others.

Metformin versus insulin

Two RCTs (Hague 2003⁸⁵ and Moore 2007⁵³) and two cohort studies (Terti 2008⁵⁶ and Balani 2008⁸⁹) examined the rate of hyperbilirubinaemia in general. Only the observational study published as an abstract (Balani 2008⁸⁹) found significantly more hyperbilirubinaemia with insulin than with metformin (*Figure 25*).

Two RCTs (Hague 2003⁸⁵ and Rowan 2008⁸⁸) and two cohort studies (Coetzee 1986⁷⁰ and Terti 2008⁵⁶) examined the rates of hyperbilirubinaemia requiring phototherapy for metformin versus insulin. *Figure 25* shows that there was no significant difference between the two groups in any study.

TABLE 14 Acceptability of treatment

| Study | Treatment discontinued because of adverse effects | Preference |
|-----------------------------|---|---|
| Glibenclamide | | |
| Chmait 2004 ⁷⁹ | | Women preferred glibenclamide (none chose insulin) – no information on post-treatment satisfaction |
| Holt 2008 ⁵² | One woman changed from glibenclamide to insulin because of hypoglycaemia and two for other side effects (not specified) In Nasruddin (2009) ⁷² three changed because of unpredictable hypoglycaemia and four for other unspecified reasons | Women treated with glibenclamide felt that their treatment was both convenient and satisfactory The doctors in the clinic felt that there was less flexibility with glibenclamide because of its long action and therefore it was harder to control the hyperglycaemia |
| Jacobson 2005 ⁷⁵ | ~ 19 women (8%) stopped glibenclamide (either switching to insulin or continuing without treatment) for reasons primarily attributed to hypoglycaemia | |
| Kahn 2006 ⁶³ | Two women were switched from glibenclamide to insulin because of recurrent hypoglycaemia (BG < 3.3 mmol/l despite dietary manipulation) | |
| Rochon 2006 ⁸³ | One woman was switched from glibenclamide to insulin because of symptomatic hypoglycaemia and one because of patient preference | |
| Metformin | | |
| Balani 2008 ⁸⁹ | 11 women stopped taking metformin (intolerance in four, refusal to continue in seven) | |
| Coetzee 1986 ⁷⁰ | Two women on metformin stopped treatment because of gastrointestinal side effects; lactic acidosis was not seen | |
| Rowan 2008 ⁸⁸ | Seven women (1.9%) on metformin stopped treatment because of gastrointestinal side effects 32 women (8.8%) on metformin had their dose reduced because of gastrointestinal side effects (but 31 maintained a dose of at least 1000 mg/day) Seven women in the metformin group and three women in the insulin group stopped treatment because of withdrawing consent No significant difference in maternal serious adverse events (infection, surgery, pelvic arthropathy) No significant difference in neonatal infection requiring hospitalisation | Questionnaire data indicated that women preferred metformin to insulin Significantly more medication adherence in the insulin than in the metformin group ($p < 0.001$) |

Small for gestational age (< 10th percentile)

Glibenclamide versus insulin

One RCT reported an RR of 0.22 (95% CI 0.01 to 4.45) for SGA (Figure 26).

None of three cohort studies found a significant difference between the treatment groups [RR 0.78 (95% CI 0.42 to 1.45), no significant heterogeneity]. Between 0% and 13% of neonates were SGA.

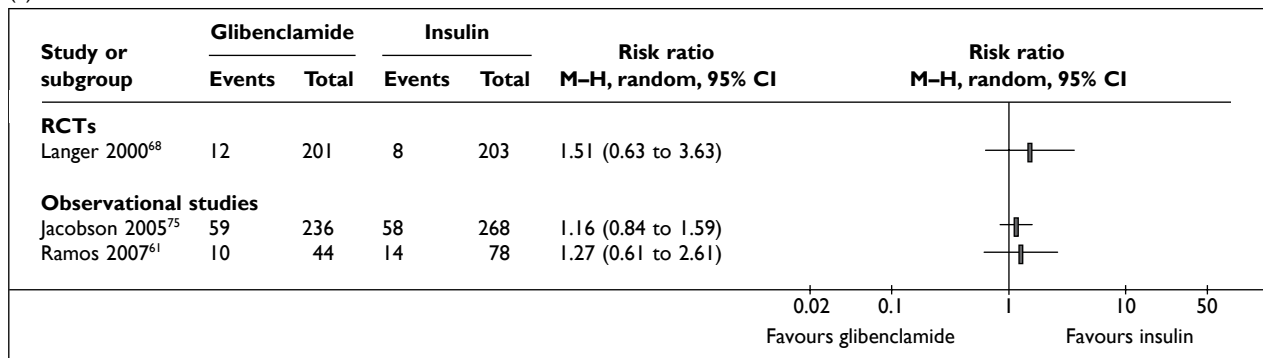
Acarbose versus insulin

No significant difference in rates of SGA neonates was seen in the trial by Bertini (2005)⁶⁷ when comparing acarbose with insulin (0% with acarbose and 7% with insulin) – see Figure 27.

Metformin versus insulin

One RCT and two cohort studies examined the effect of metformin versus insulin on rates of SGA neonates (Figure 28). None of the studies found a significant difference between the treatment groups. The RR was 0.74 (95% CI 0.45 to 1.19) for the RCT and 1.39 (95% CI 0.56 to 3.50) for the

(a)



(b)

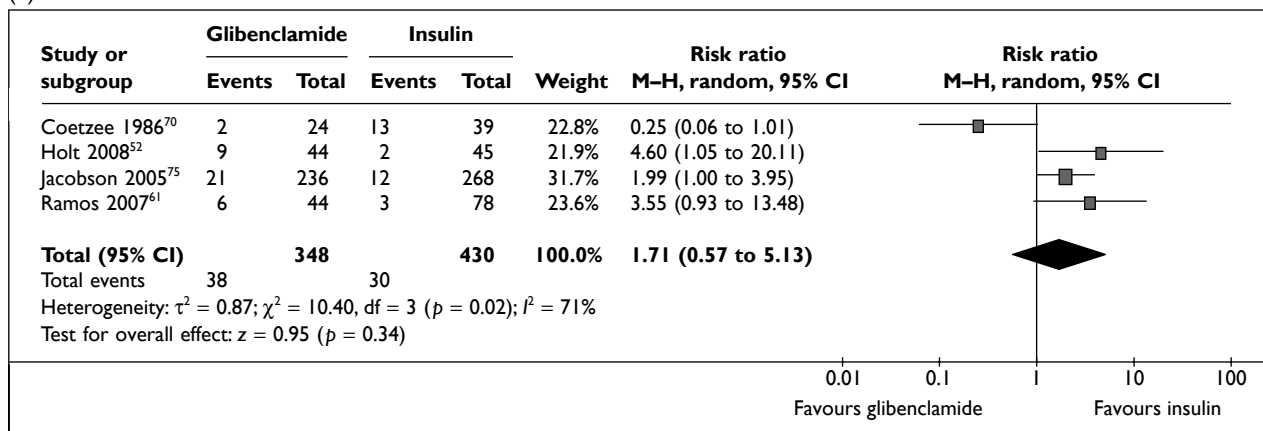


FIGURE 24 (a) Hyperbilirubinaemia/need for; (b) phototherapy: glibenclamide versus insulin.

observational studies (no significant heterogeneity). Between 2% and 19% of neonates were SGA.

Neonatal ICU admission

Glibenclamide versus insulin

One RCT found no difference in NICU admission (RR 0.87, 95% CI 0.41 to 1.83).

Of six cohort studies reporting on NICU admission after treatment with glibenclamide or insulin (Figure 29 and below) only one, Jacobson (2005),⁷⁵ found significantly more NICU admission in the insulin group than in the glibenclamide group (24% vs 15%, $p = 0.008$); however, NICU length of stay was significantly longer in the glibenclamide group (8.0 ± 10.1 days vs 4.3 ± 9.6 days with insulin, $p = 0.002$). None of the other studies found a significant difference, and there was no significant difference overall [0.75 (95% CI 0.53 to 1.05)]. The rate of NICU admission was between 6% and 25%. Other studies: Fines (2003),⁷² Goodman (2008)⁷⁴ and Langer (2006),⁷⁶ found no significant differences.

Acarbose versus insulin

Bertini (2005)⁶⁷ found no NICU admissions when comparing acarbose with insulin groups.

Metformin versus insulin

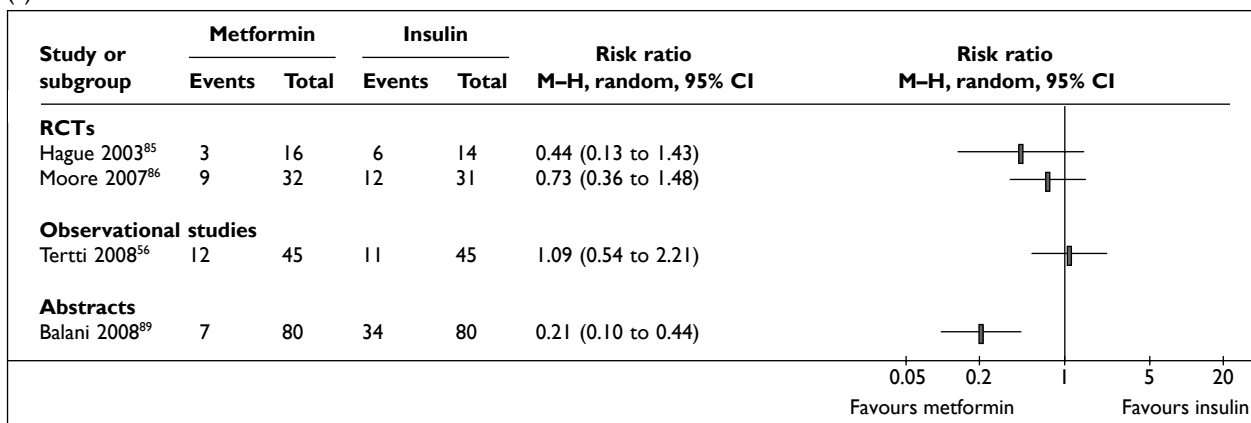
Two RCTs reported no difference in NICU admissions or length of stay (Figure 30).

One cohort study by Balani (2008),⁸⁹ published as an abstract, found significantly more admission to the NICU in the insulin group than in the metformin group (19% vs 5%, $p = 0.01$). The other, Terti (2008),⁵⁶ found no significant difference in treatment days spent at the NICU although the CIs only just overlapped with no difference (RR 0.68, 95% CI 0.45 to 1.02).

Congenital malformations

The presence of congenital malformation might suggest pre-existing diabetes rather than GDM, since the key period for teratogenesis is in the first trimester. However, we give the figures below for reassurance.

(a)



(b)

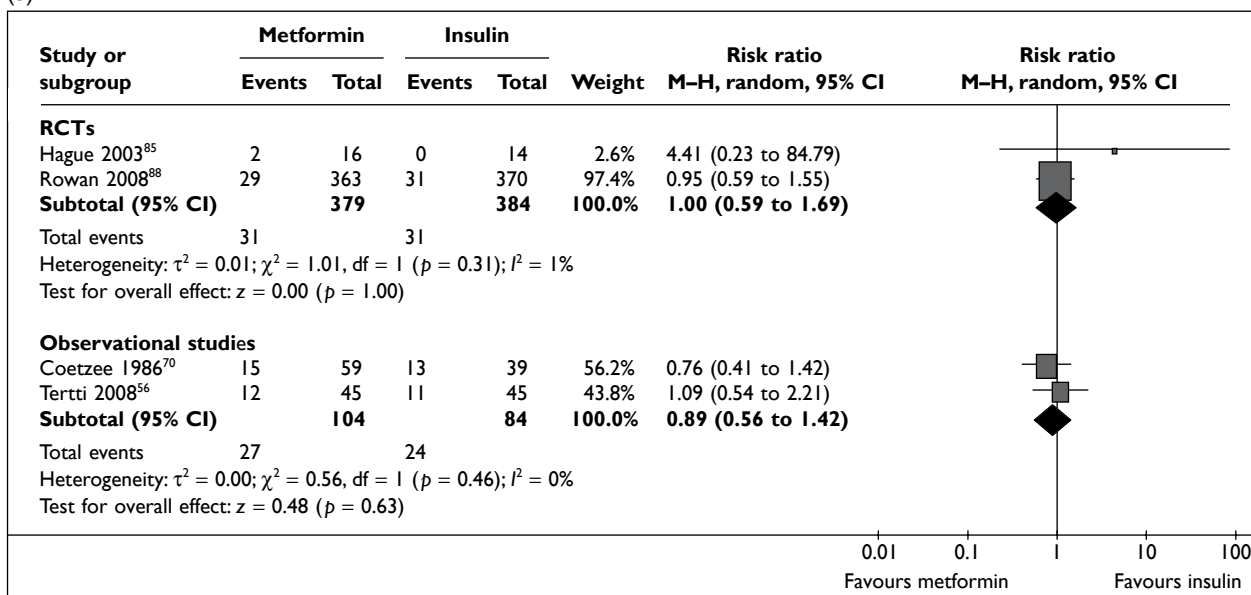


FIGURE 25 (a) Hyperbilirubinaemia/need for; (b) phototherapy: metformin versus insulin.

Glibenclamide versus insulin

Two RCTs and three cohort studies reported congenital malformations or anomalies after treatment with glibenclamide or insulin (Figure 31). There were no significant differences in congenital malformations or anomalies between the comparison groups (rates of malformations/anomalies 0% to 10%). In the study by Ramos (2007),⁶¹ congenital abnormalities for infants in the glibenclamide group included patent ductus arteriosus, ventricular septal defect, atrial septal defect, inguinal hernias, intestinal atresia and spine anomaly. No details were reported in the other studies.

Metformin versus insulin

One RCT and three cohort studies reported congenital malformations or anomalies after treatment with metformin or insulin (see Figure 32 and below). There were no significant differences in congenital malformations or anomalies between the comparison groups (rates of malformations/anomalies 0% to 10%). Other studies: Balani (2008)⁸⁹ showed no significant difference in rate of congenital malformations.

Respiratory distress

Glibenclamide versus insulin

The Langer (2000)⁶⁸ RCT reported no difference between groups, and the Bertini (2005)⁶⁷ trial reported that there were no reports of respiratory

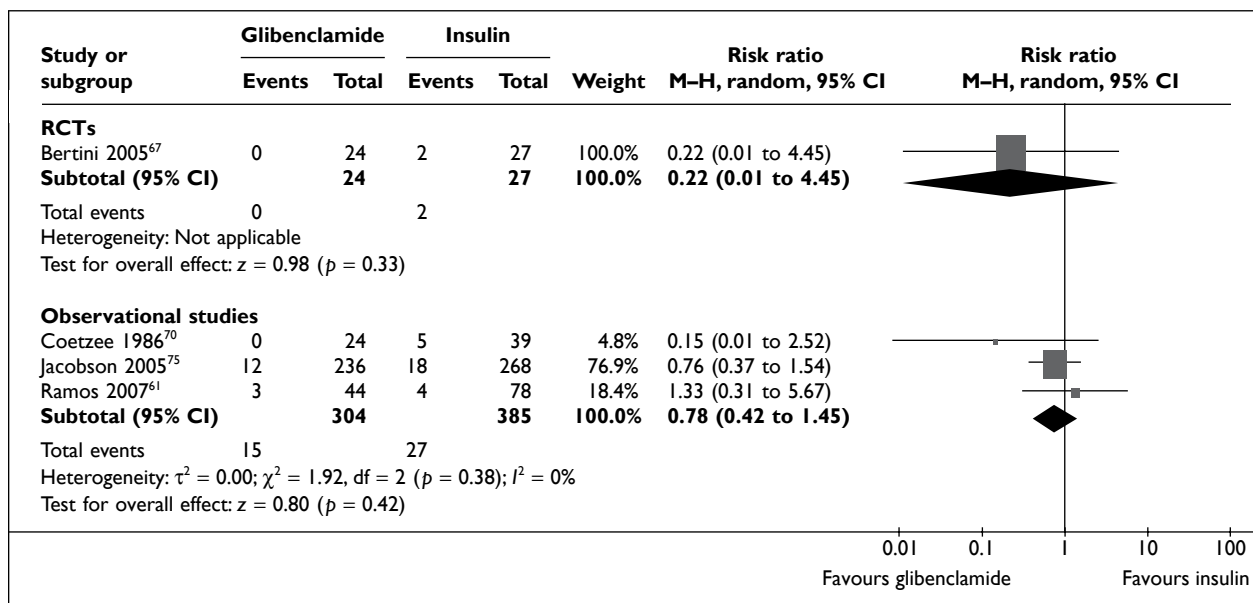


FIGURE 26 SGA: glibenclamide versus insulin.

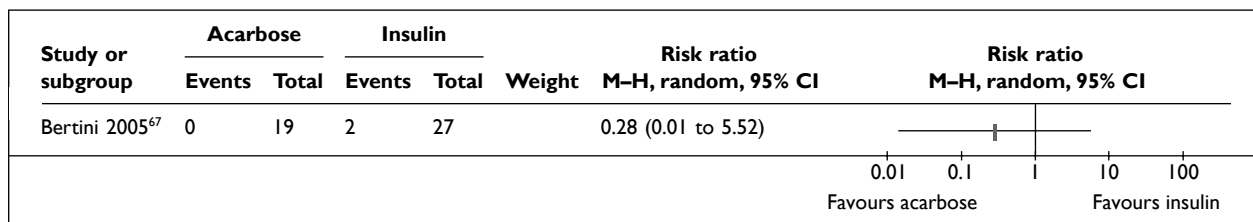


FIGURE 27 SGA: acarbose versus insulin.

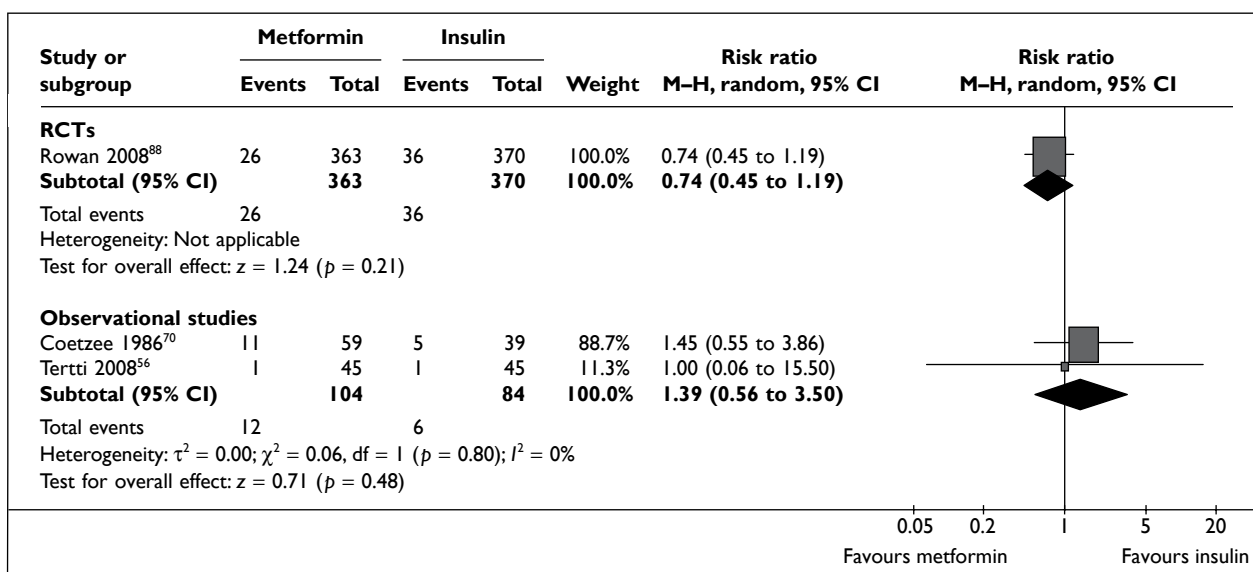


FIGURE 28 SGA: metformin versus insulin.

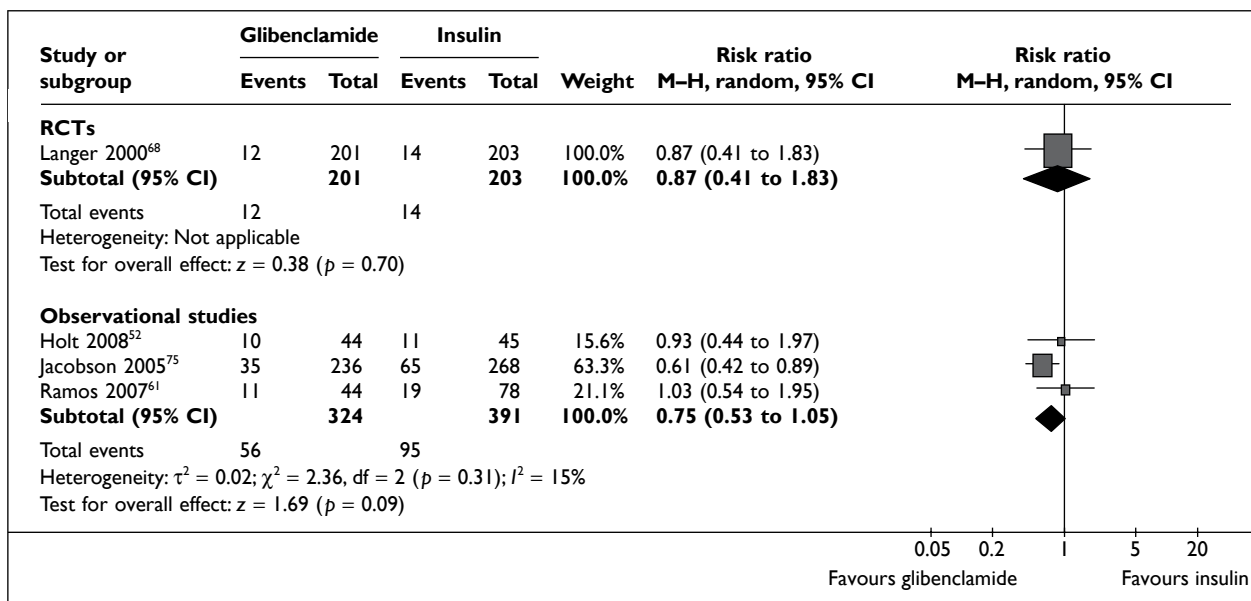


FIGURE 29 NICU admission: glibenclamide versus insulin.

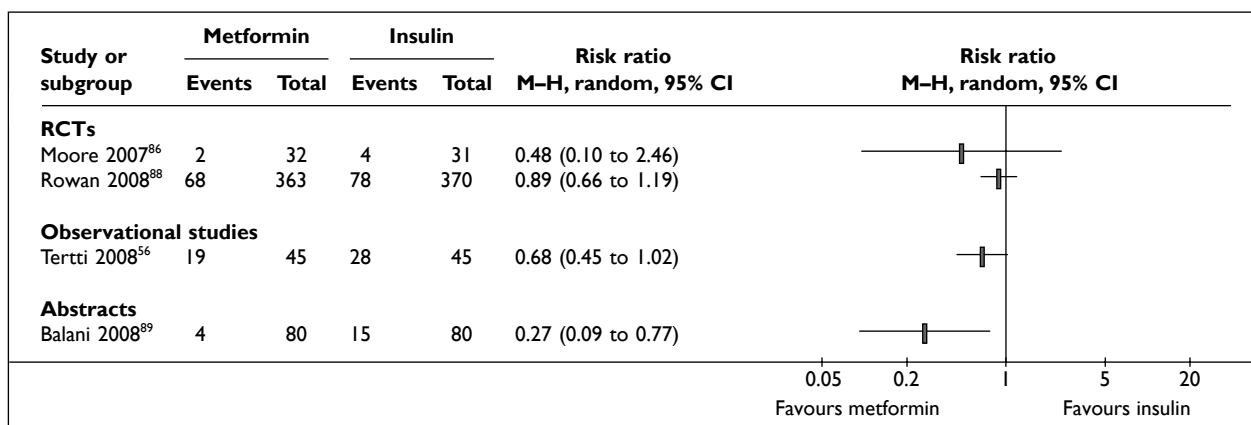


FIGURE 30 NICU admission: metformin versus insulin.

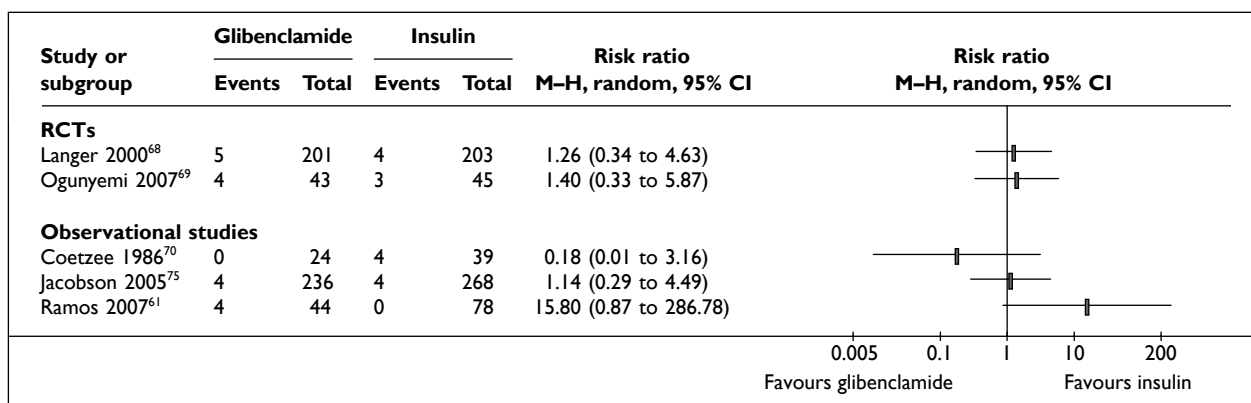


FIGURE 31 Congenital malformations/anomalies: glibenclamide versus insulin.

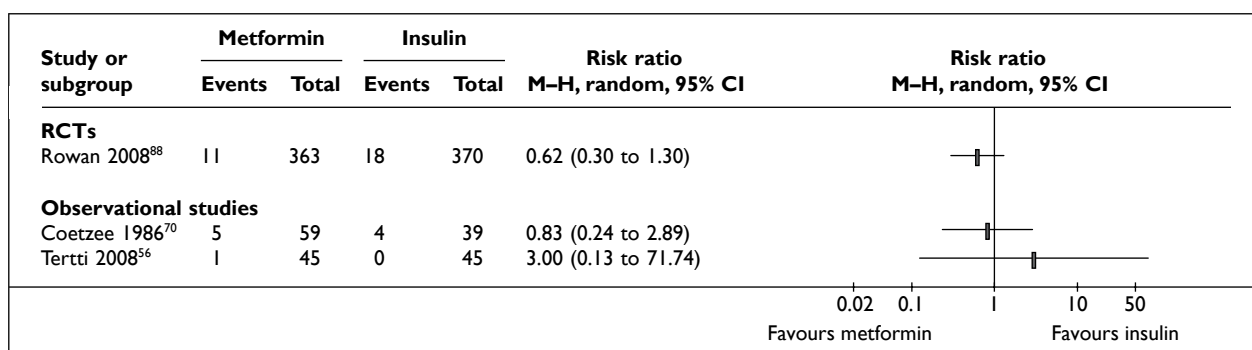


FIGURE 32 Congenital malformations/anomalies: metformin versus insulin.

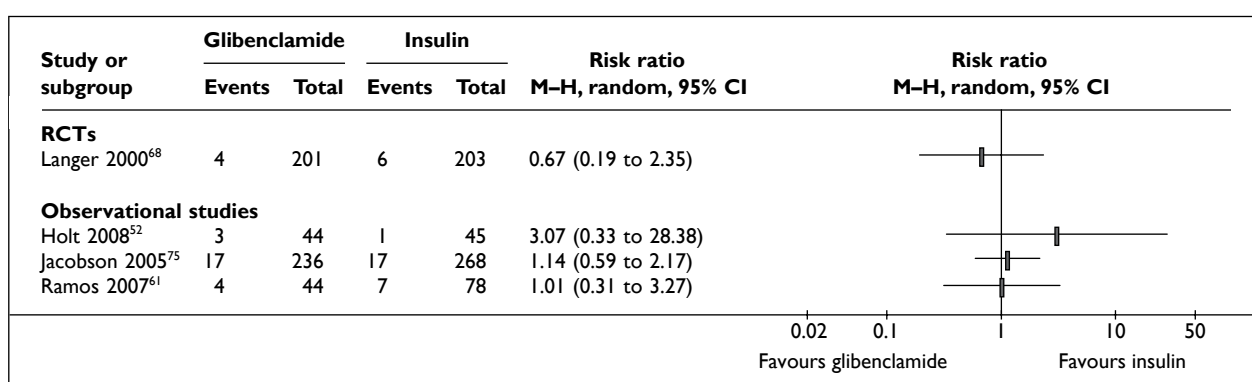


FIGURE 33 Respiratory distress/respiratory support: glibenclamide versus insulin.

distress in the glibenclamide group (insulin not reported).

Langer (2000)⁶⁸ reported lung complications in 8% of infants in the glibenclamide group and 6% of infants in the insulin group (no significant difference).

Four cohort studies reported on respiratory distress (Holt 2008⁵²) and oxygen/assisted ventilation (Jacobson 2005⁷⁵ and Ramos 2007⁶¹) (Figure 33). None of the studies reported a significant difference between groups (rates 2–9%)

Metformin versus insulin

Two RCTs reported no differences in respiratory distress after treatment with metformin or insulin. One cohort study reported the same (Figure 34).

Apgar scores

Glibenclamide versus insulin

Apgar scores at 1 and 5 minutes were reported by one RCT and four cohort studies (see Figure 35 and below). Holt (2008)⁵² found a significantly higher

1-minute Apgar score in the insulin group than in the glibenclamide group (8.2 vs 7.3, $p = 0.05$). The RCT by Bertini (2005)⁶⁷ found a significantly higher 5-minute Apgar score (9.4 vs 9.0, $p = 0.03$) in the insulin group than in the glibenclamide group.

The Fines (2003),⁷² Goodman (2008)⁷⁴ and Paterson (2008)⁷⁷ studies reported no significant differences in any Apgar scores.

Acarbose versus insulin

Bertini (2005)⁶⁷ did not find any significant differences in Apgar scores at 1 or 5 minutes between the acarbose and the insulin groups. Apgar scores at 1 minute were between 8.1 and 8.4, and Apgar scores at 5 minutes were between 9.3 and 9.4 (Figure 36).

Metformin versus insulin

In the RCT by Rowan (2008),⁸⁸ three neonates in the metformin group (0.8%) and one (0.3%) in the insulin group had 5-minute Apgar scores below 7; all these infants had Apgar scores of 6.

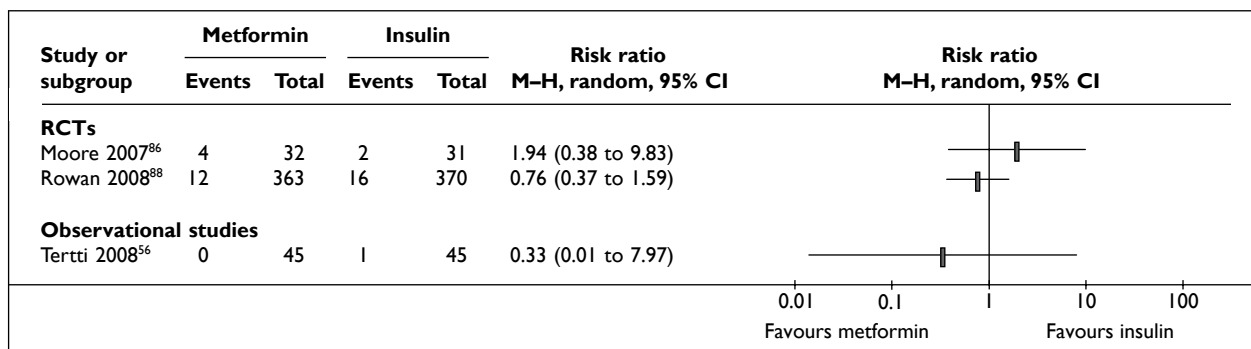


FIGURE 34 Respiratory distress: metformin versus insulin.

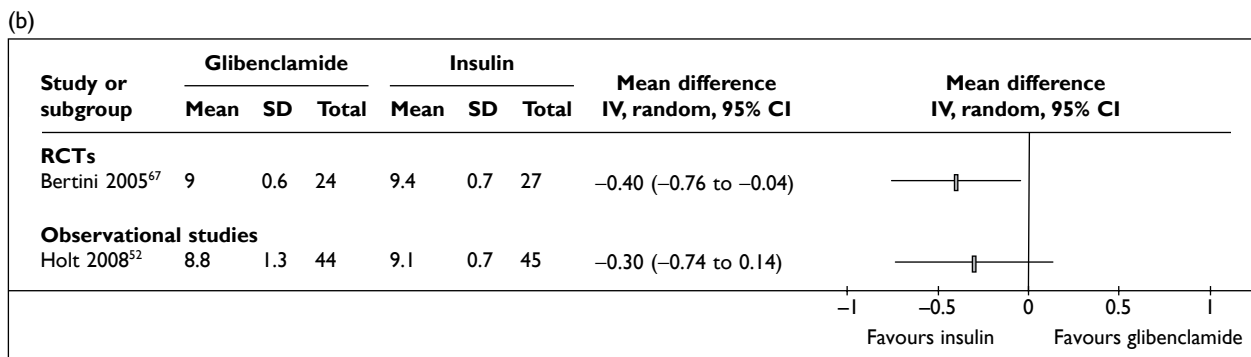
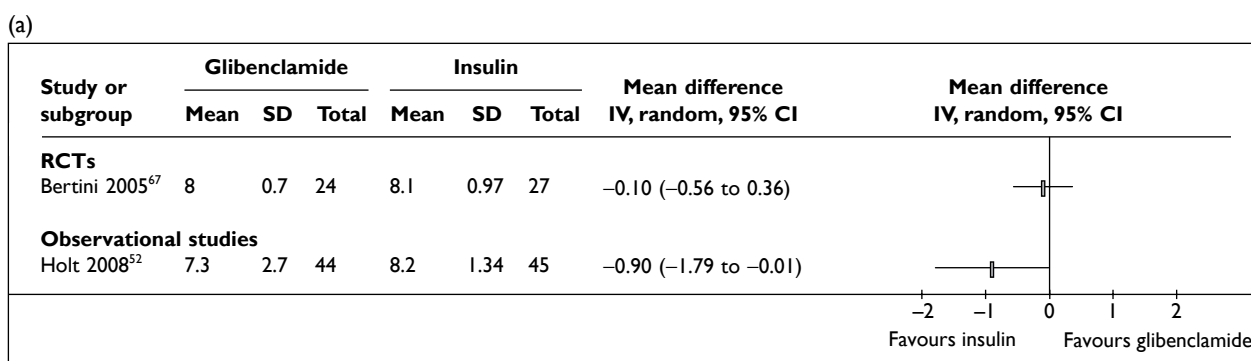


FIGURE 35 Apgar scores: glibenclamide versus insulin. (a) 1-minute Apgar score; (b) 5-minute Apgar score.

Apgar scores at 5 minutes were reported by one RCT and one cohort study (Figure 37). None of the studies found a significant difference between metformin and insulin. Mean Apgar scores at 5 minutes ranged from 8.6 to 9.0.

Timing of delivery

Glibenclamide versus insulin

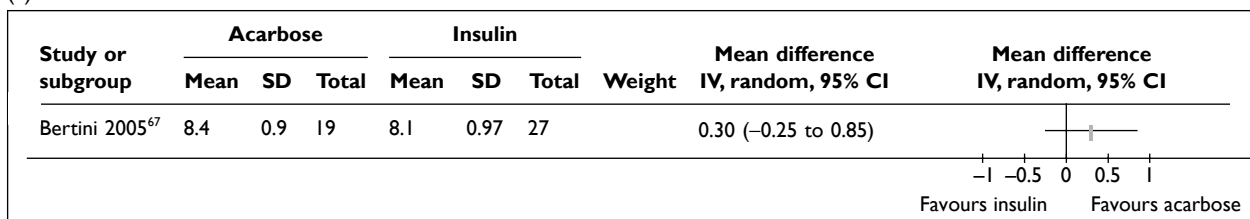
The RCT by Bertini (2005)⁶⁷ reported that there were no reports of prematurity in the glibenclamide group (insulin not reported), and two cohort studies (Figure 38) found no significant difference between comparison groups.

Three RCTs and five cohort studies reported on gestational age at delivery (see Figure 39, Duncan 2005⁷¹ and Goodman 2008⁷⁴) reported no significant differences between the glibenclamide and the insulin groups (WMD -0.06 weeks, 95% CI -0.26 to 0.15) (no significant heterogeneity). Gestational age at delivery ranged from 37.6 to 39 weeks.

Acarbose versus insulin

Rates of preterm deliveries for acarbose versus insulin were not reported. The age of gestation at delivery was 38.2 ± 1.2 weeks in the acarbose group

(a)



(b)

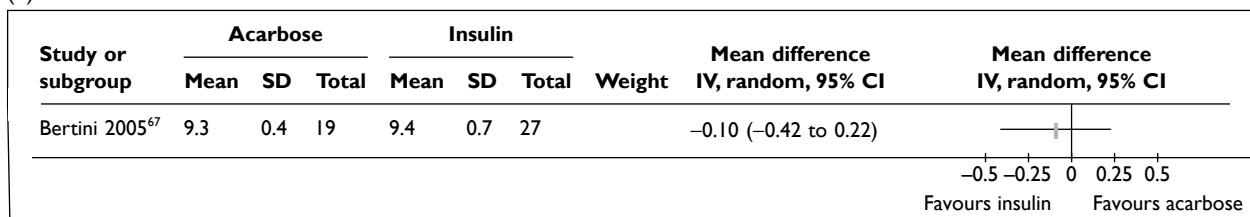


FIGURE 36 Apgar scores: acarbose versus insulin. (a) 1-minute Apgar score; (b) 5-minute Apgar score.

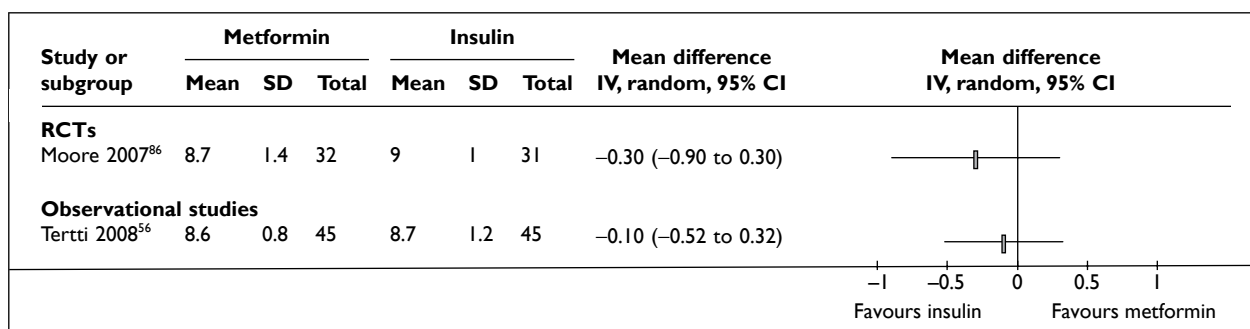


FIGURE 37 5-minute Apgar score: metformin versus insulin.

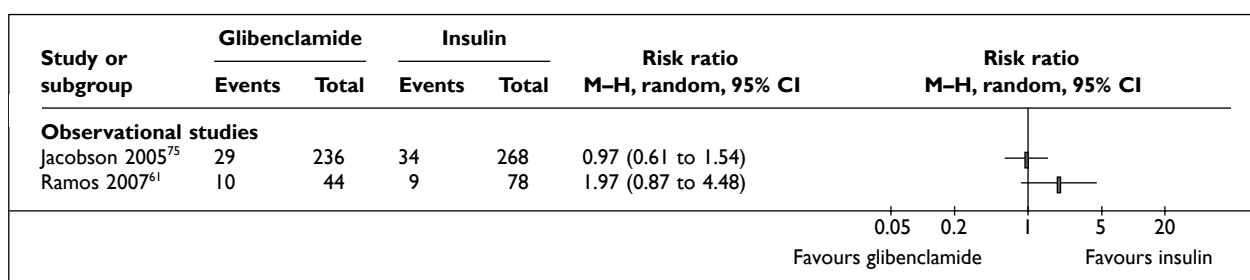


FIGURE 38 Preterm delivery: glibenclamide versus insulin.

and 38.5 ± 1.2 weeks in the insulin group (no significant difference).

Metformin versus insulin

One RCT and two cohort studies reported on premature deliveries after treatment with metformin or insulin (Figure 40). Rowan (2008)⁸⁸ found a significantly higher rate of preterm

delivery with metformin than with insulin (12.1% vs 7.6%, $p = 0.04$); in both groups, about half the preterm births were iatrogenic (indicated) and half were spontaneous.

The cohort study by Balani (2008),⁸⁹ published only as an abstract, found significantly more preterm deliveries in the insulin group than in

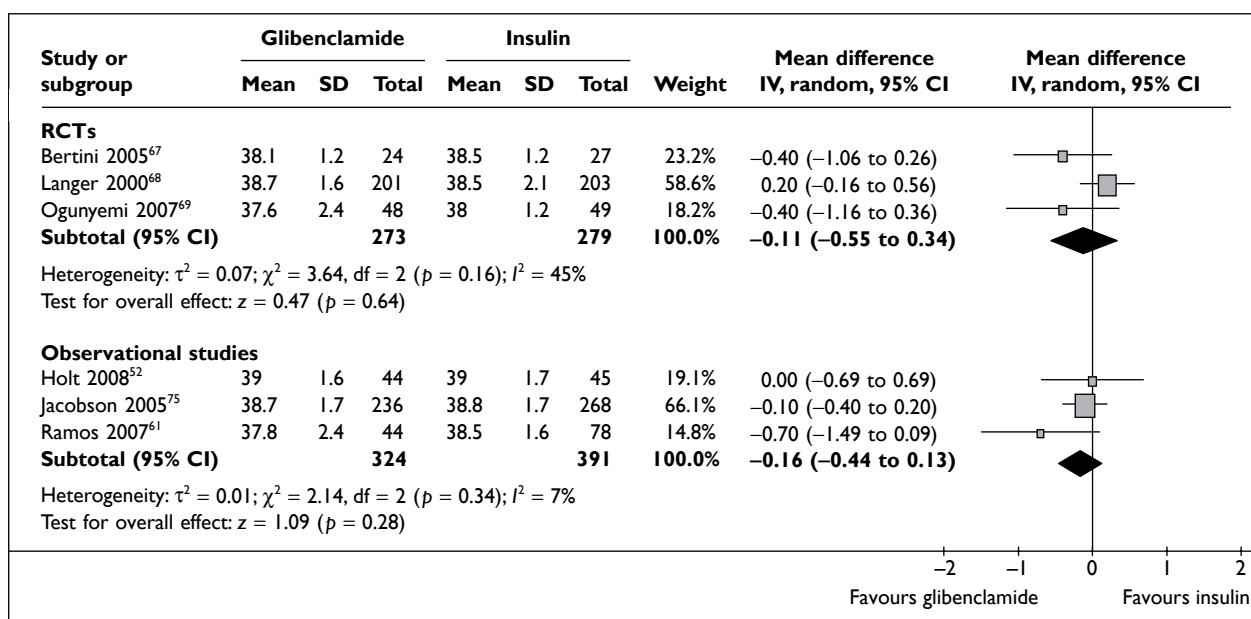


FIGURE 39 Gestational age at delivery.

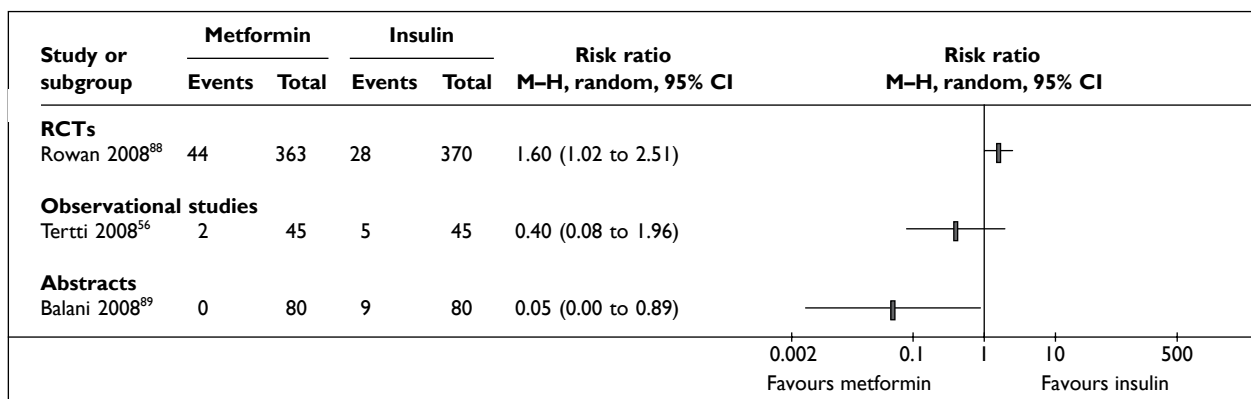


FIGURE 40 Preterm delivery: metformin versus insulin.

the metformin group (0% vs 11%, $p < 0.01$). No significant difference in premature deliveries between groups was observed in the study by Tertti (2008).⁵⁶

Three RCTs reported on gestational age at delivery (Figure 41). A meta-analysis of the RCTs showed a significant difference ($p = 0.03$) of -0.21 weeks (95% CI -0.40 to -0.02) lower gestational age with metformin compared with the insulin group.

One observational study (Tertti 2008⁵⁶) showed a non-significant difference of 3 weeks' older gestational delivery with metformin.

Other outcomes/data

Appendix 9 contains information on additional outcomes reported within studies included within this review. In addition, Appendix 9 also contains information from studies which did not meet the inclusion criteria for our review but nevertheless are of interest with respect to the treatment of hyperglycaemia in pregnancy.

Glibenclamide versus metformin

The small RCT by Moore (2005),⁹⁵ reported as an abstract, studied 46 women with gestational diabetes treated either with metformin ($n = 22$) or glibenclamide ($n = 24$) (Table 15).

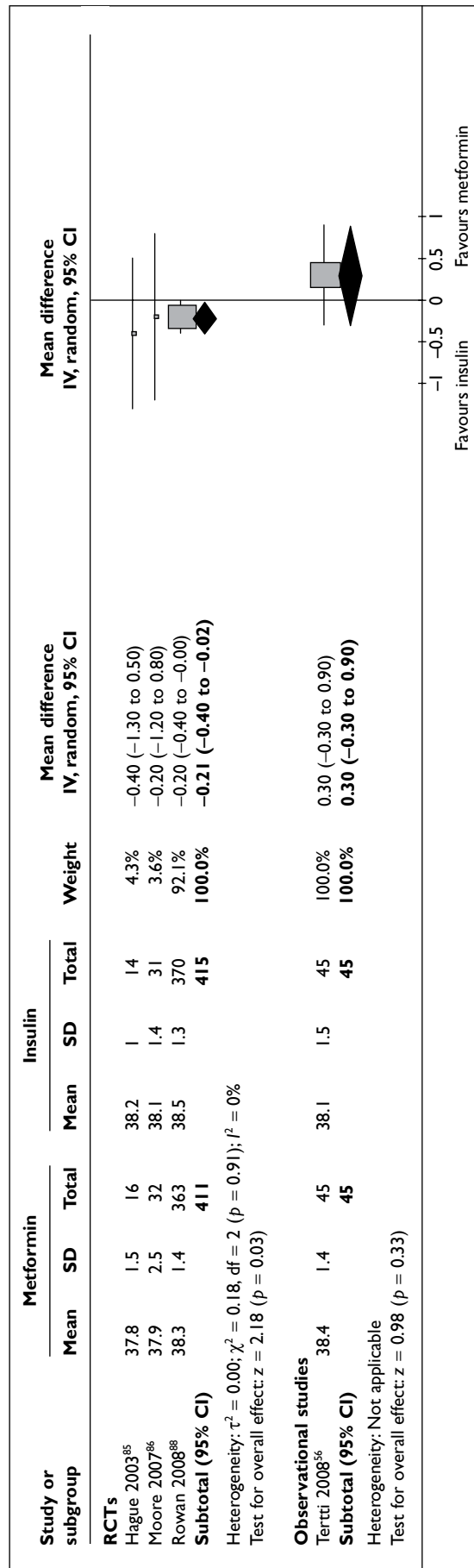


FIGURE 41 Gestational age at delivery: metformin versus insulin.

TABLE 15 Results of the Moore (2008)⁹⁶ RCT of metformin versus glibenclamide

| Outcome | Metformin | n | Glibenclamide | n | p |
|--|-----------|----|---------------|----|------|
| Maternal | | | | | |
| Treatment failure | 41.2% | 63 | 19.6% | 61 | 0.01 |
| Severe pre-eclampsia | n=2 | 63 | n=3 | 61 | NS |
| Caesarean delivery (non-elective) | n=11 | 63 | n=2 | 61 | 0.02 |
| FBG (mmol/l ± SD) | 5.1 ± 0.7 | 22 | 5.0 ± 0.4 | 24 | NS |
| 2-hour PPG breakfast (mmol/l ± SD) | 5.6 ± 0.8 | 22 | 5.4 ± 0.4 | 24 | NS |
| 2-hour PPG lunch (mmol/l ± SD) | 5.9 ± 0.8 | 22 | 6.6 ± 0.8 | 24 | NS |
| 2-hour PPG dinner (mmol/l ± SD) | 6.1 ± 0.8 | 22 | 6.1 ± 0.4 | 24 | NS |
| Maternal hypoglycaemia (BG < 3.3 mmol/l) | n=2 | 63 | n=1 | 61 | NS |
| Neonatal | | | | | |
| Neonatal hypoglycaemia | n=1 | 63 | 0 | 61 | NS |
| Hyperbilirubinaemia | | 22 | | 24 | NS |
| Macrosomia | n=1 | 63 | n=4 | 61 | NS |
| NICU admission | n=4 | 63 | n=1 | 61 | NS |
| Shoulder dystocia | 0 | 63 | n=1 | 61 | NS |
| Respiratory distress | | 22 | | 24 | NS |
| 5-minute Apgar score < 7 | 0 | 63 | 0 | 61 | NS |
| NS, not significant. | | | | | |

No significant differences between the groups were seen in glycaemic control or outcomes. Another abstract by Moore (2008)⁹⁶ appears to present an extension of the RCT previously reported, now with 63 patients on metformin and 61 on glibenclamide (see Table 10). Outcomes remain similar, apart from there being more non-elective caesarean deliveries with metformin than with glibenclamide [17% (three breech presentation, eight non-reassuring fetal status) vs 3% (one failure to progress, one non-reassuring fetal status), $p = 0.02$].

Oral medication failure

The issue here is whether it is possible to predict failure on oral agents, in which case they would not be used, but patients would go straight to insulin once diet and physical activity failed.

Appendix 10 contains details of studies considering failure of oral medication.

Failure to achieve adequate glycaemic control on glibenclamide

Between 4% and 24% of women receiving glibenclamide were considered to fail treatment and were switched to insulin. The RCT by Langer (2000)⁶⁸ reported that 4% of patients in the

glibenclamide group were switched to insulin because of glibenclamide failure. However, 18% of women in the glibenclamide group had self-monitored BG values that were not in the desired range. The cohort study by Langer (2006)⁸¹ suggested that glibenclamide failure was also related to glibenclamide dose: with a dose of less than 10 mg/dl, 60% achieved mean BG targets and 76% achieved 2-hour PPG targets, while when including patients receiving a dose of more than 10 mg/dl, 85% achieved target glycaemic control ($p = 0.00002$ for dose effect).

Most studies did not report whether glycaemic control was adequate with insulin. However, data from some studies suggest that control with insulin was not necessarily more reliable. Langer (2000)⁶⁸ report that 12% of women in the insulin group had self-monitored BG values that were not in the desired range. When studying glycaemic values of a subsample of 122 women on glibenclamide and 137 women on insulin in their cohort study, Jacobson (2005)⁷⁵ found that mean fasting and/or post-prandial values were within goal for 86% in the glibenclamide group but only for 63% in the insulin group ($p < 0.001$). Gilson (2002)⁷³ reported similar numbers of patients not achieving adequate

control with glibenclamide or insulin. While Holt (2008)⁵² reported that all of the women switched to insulin because of glibenclamide failure achieved adequate control, Conway (2004)⁸⁰ reported that 67% of the patients switched to insulin also failed to achieve adequate control with insulin, as did 55% of glibenclamide failures in the study by Kahn (2006).⁶³

Failure to achieve adequate glycaemic control on metformin

Of the metformin studies, Moore (2007)⁵³ reported no cases of metformin failure, while Terti (2008)⁵⁶ reported a failure rate of 18%. In the RCT by Rowan (2008)⁸⁸ 46.3% of women on metformin required supplemental insulin, and in the study by Balani (2008)⁸⁹ 11% of participants on metformin required additional insulin. In the RCT by Moore (2008),⁸⁶ comparing metformin with glibenclamide, significantly more women failed metformin therapy than glibenclamide therapy (41.2% vs 19.6%, $p = 0.01$). None of the studies reported whether adequate control was achieved with insulin.

Factors associated with failure to achieve adequate glycaemic control on oral medication

Only five studies (Holt 2008,⁵² Kahn 2006,⁶³ Chmait 2004,⁷⁹ Conway 2004⁸⁰ and Rochon 2006,⁸³ all cohort studies) reported some comparison data for glibenclamide success versus glibenclamide failure groups, and only the RCT by Rowan (2008)⁸⁸ compared characteristics of women with adequate control on metformin alone and women requiring supplemental insulin. The factors analysed most frequently were maternal age, parity, maternal BMI, history of gestational diabetes, family history of diabetes mellitus, gestational age at diagnosis of gestational diabetes, and results of the OGTT. Maternal and neonatal outcomes following treatment for those studies (Kahn 2006,⁶³ Chmait 2004,⁷⁹ Conway 2004⁸⁰ and Rochon 2006⁸³) only comparing glibenclamide-only groups with those switching to insulin are reported above.

Maternal age

Six studies (Chmait 2004,⁷⁹ Conway 2004,⁸⁰ Kahn 2006,⁶³ Rochon 2006,⁸³ Holt 2008,⁵² Langer 2006⁸¹) reported maternal age for glibenclamide failure and glibenclamide success groups. Kahn (2006)⁶³ found that mothers in the glibenclamide failure group were significantly older than mothers in the success group (mean difference 5 years, 95% CI 2.43 to 7.57). Langer (2006)⁸¹ reported that older age was a predictor of failure but gave little detail.

The other four studies found no difference. The age range in the failure groups was 31–34 years, and in the success groups 29–32 years.

Parity

Four studies (Chmait 2004,⁷⁹ Kahn 2006,⁶³ Conway 2004,⁸⁰ Rochon 2006⁸³) reported on parity or number of multiparous women for glibenclamide failure versus glibenclamide success. There was a tendency for higher parity and a larger proportion of multiparous women in the failure group; however, this only reached significance in the study by Kahn (2006)⁶³ (parity 2 ± 1.7 in the failure group vs 1 ± 1 in the success group, $p = 0.03$; similar result for gravidity). Parity was between 2 and 2.2 in the failure groups and 1 and 1.7 in the success groups. Between 86% and 92% in the failure groups and 70% and 86% in the success groups were multiparous.

In the RCT by Rowan (2008),⁸⁸ significantly more women requiring supplementary insulin were multiparous than women with adequate control on metformin only (76% vs 61.5%, $p = 0.003$).

Maternal BMI

Maternal BMI was reported in three studies comparing glibenclamide failure with glibenclamide success. One of those studies found a significantly higher BMI in the failure group than in the success group (33.2 ± 5.4 vs 28.8 ± 5.8 kg/m², $p = 0.02$). BMI was between 32 and 33.2 kg/m² in the failure groups and between 28.8 and 31.5 kg/m² in the success groups. Langer (2006)⁸¹ found no significant difference in obesity between glibenclamide failure and success groups.

Rowan (2008)⁸⁸ reported significantly higher BMI values (in early pregnancy) for those requiring additional insulin than those with adequate control on metformin alone (33.6 ± 8.6 vs 31.1 ± 7.8 kg/m², $p = 0.01$). BMI values at enrolment were also significantly higher in those requiring supplemental insulin ($p < 0.001$).

History of gestational diabetes

None of five studies (Chmait 2004,⁷⁹ Conway 2004,⁸⁰ Kahn 2006,⁶³ Rochon 2006,⁸³ Parrish 2008⁸²) found a significant difference in rates of history of gestational diabetes between the failure and the success groups (RR 1.42, 95% CI 0.85 to 2.37 for full publications). Rates of history of previous gestational diabetes ranged between 14% and 58% in the failure groups and 13% and 41% in the success groups.

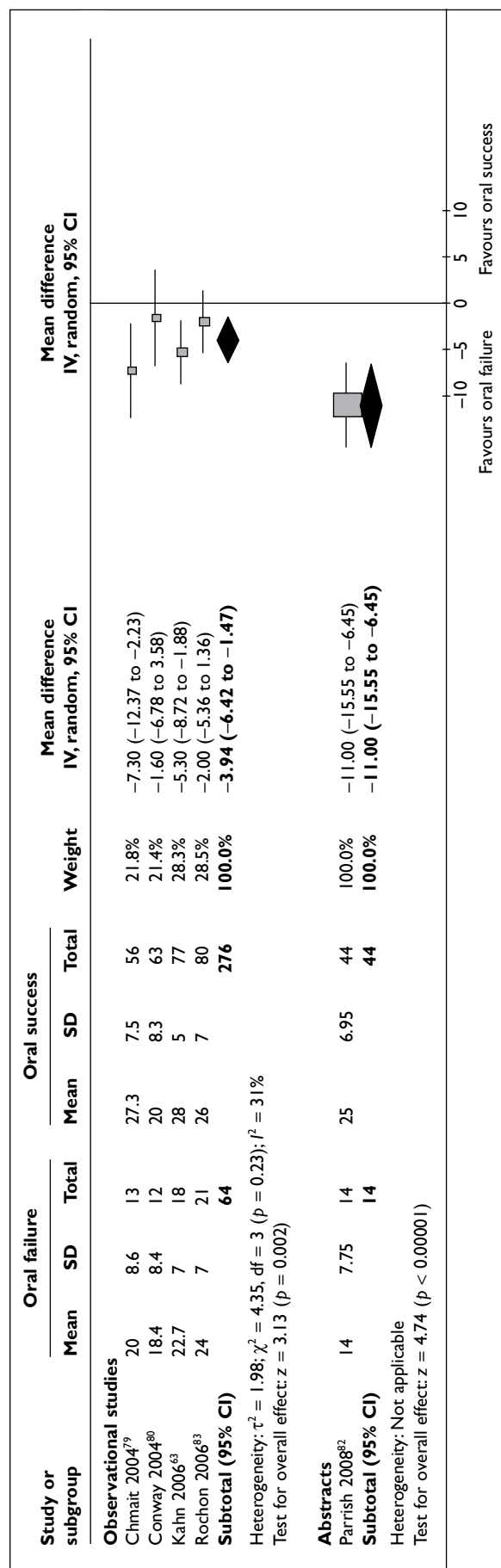


FIGURE 42 Gestational age (weeks) at GDM diagnosis: oral failure versus oral success.

The RCT by Rowan (2008)⁸⁸ reported significantly higher rates of history of gestational diabetes for those requiring additional insulin than for those with adequate control on metformin alone (33.3% vs 19.5%, $p = 0.009$).

Family history of diabetes

Four studies (Chmait 2004,⁷⁹ Conway 2004,⁸⁰ Rochon 2006,⁸³ Parrish 2008⁸²) reported on family history of diabetes mellitus in women failing glibenclamide versus those with adequate glycaemic control with glibenclamide. Three of the studies found no significant difference in rates of family history of diabetes between the failure and the success groups (in their original analyses). In the study by Rochon (2006),⁸³ marginally more women with a family history of diabetes were seen in the success group than in the failure group (52% vs 14%, $p = 0.076$ in the original analysis). Rates of family history of diabetes were between 14% and 93%.

The RCT by Rowan (2008)⁸⁸ reported significantly higher rates of women with a maternal family history of diabetes among those requiring additional insulin compared with those with adequate control on metformin alone (52.4% vs 38.0%, $p = 0.006$).

Gestational age at diagnosis

Four observational studies (*Figure 42*) found that women failing glibenclamide were diagnosed at a significantly earlier gestational age (14–22.7 weeks vs 25–28 weeks, $p < 0.003$) and overall (WMD –3.94 weeks, 95% CI –6.42 to –1.47, $p = 0.002$). An abstract by Parrish (2008)⁸² showed a large difference in gestational age at diagnosis between oral success and oral failure groups (14 weeks vs 25 weeks, $p < 0.00001$).

Women were diagnosed at between 14 and 22.7 weeks of gestation in the failure group and between 20 and 28 weeks of gestation in the success group.

Glucose levels

Five studies (*Figure 43*) examined FBG on the OGTT as a predictor of glibenclamide failure. The study by Kahn (2006)⁶³ found a significant difference, with women in the failure group having significantly higher FBG values (6.22 vs 5.55 mmol/l, $p = 0.045$). The study by Langer (2006)⁸¹ published in abstract form only also found FPG to be a predictor of glibenclamide failure but provided no further data. Overall, FBG values were significantly higher in the failure group than in the

success group (WMD 0.49 mmol/l, 95% CI 0.19 to 0.79) (no significant heterogeneity). FBG values were between 5.8 and 6.4 mmol/l in the failure group and between 5.2 and 5.7 mmol/l in the success group.

Rowan (2008)⁸⁸ also found significantly higher FBG values on the OGTT for the women requiring additional insulin compared with those with adequate control on metformin alone (6.1 vs 5.3 mmol/l, $p < 0.001$). Similarly, enrolment FBG and HbA_{1c} were significantly higher in those subsequently requiring supplementary insulin ($p < 0.001$).

Three studies reported on 1-hour, 2-hour and 3-hour OGTT values in relation to glibenclamide failure or success (*Figure 44*). In their original analyses, Chmait (2004)⁷⁹ found no significant difference in the OGTT values between glibenclamide failure and success groups at any time point; Conway (2004)⁸⁰ found significantly higher values in the failure group than in the success group at all time points ($p < 0.001$), and Rochon (2006)⁸³ found significantly higher values at 1 hour in the failure group, no difference between groups for the 2-hour value, and significantly lower 3-hour values for the failure than the success group. Overall, 1-hour values were significantly higher in the failure group than in the success group (WMD 1.20 mmol/l, 95% CI 0.56 to 1.84, $p = 0.0002$), as were 2-hour values (WMD 1.11 mmol/l, 95% CI 0.44 to 1.77, $p = 0.001$); there was no significant difference for 3-hour values. Values at 1 hour ranged from 11.4 to 12.8 mmol/l in the failure group and 11.0 to 11.4 mmol/l in the success group; values at 2 hours ranged from 10.5 to 11.3 mmol/l in the failure group and 9.4 to 9.9 mmol/l in the success group; values at 3 hours ranged between 6.33 and 9.8 mmol/l.

Additionally, Holt (2008)⁵² reported that there was no difference in baseline glycaemia between the women in their study failing glibenclamide and those who did not (no values given).

Other studies: Langer (2006)⁸¹ also reported that FPG was a predictor of glibenclamide failure, $p = 0.007$.

In addition to the results presented in *Figure 44*, Chmait (2004)⁷⁹ found that there were significantly more women in the glibenclamide failure group who had had an infant with macrosomia in a previous delivery (54% vs 22%, $p = 0.02$). No significant difference in ethnicity was found.

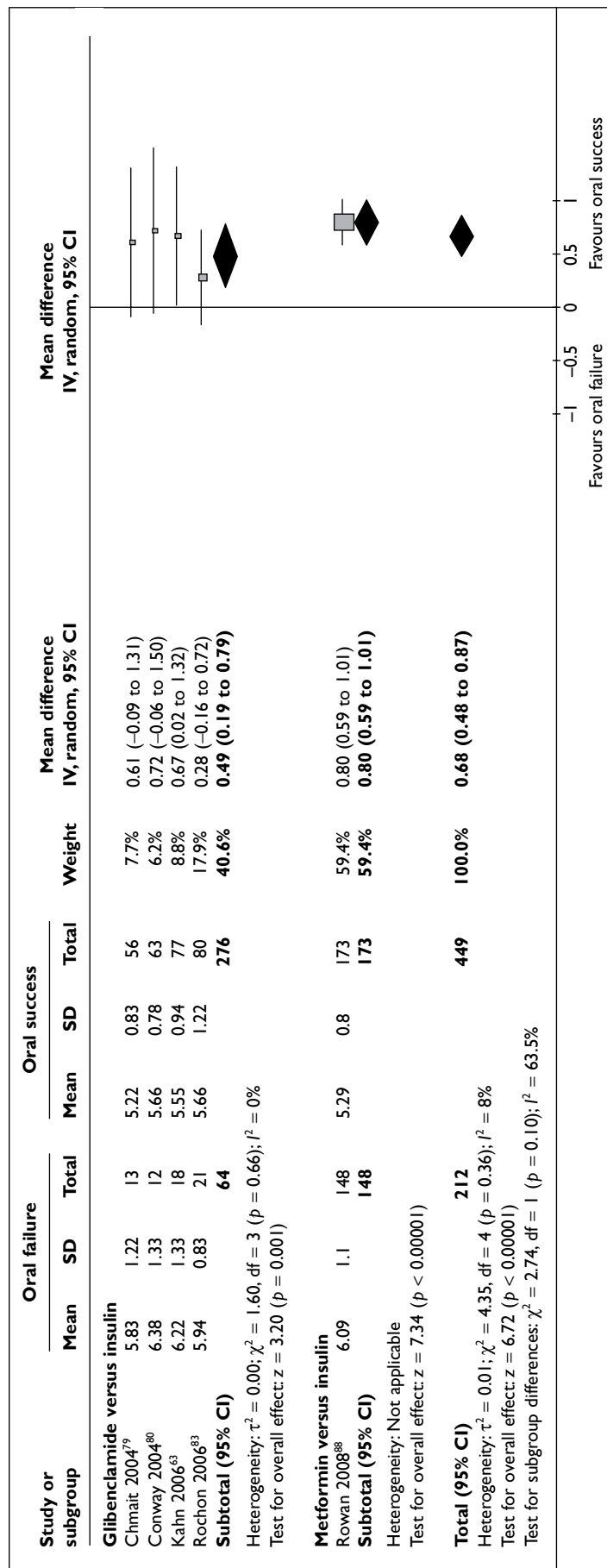
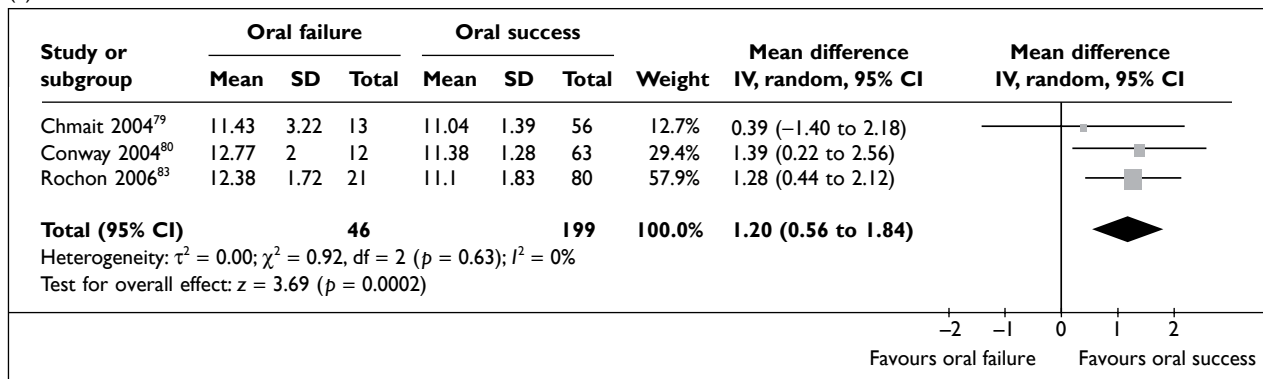
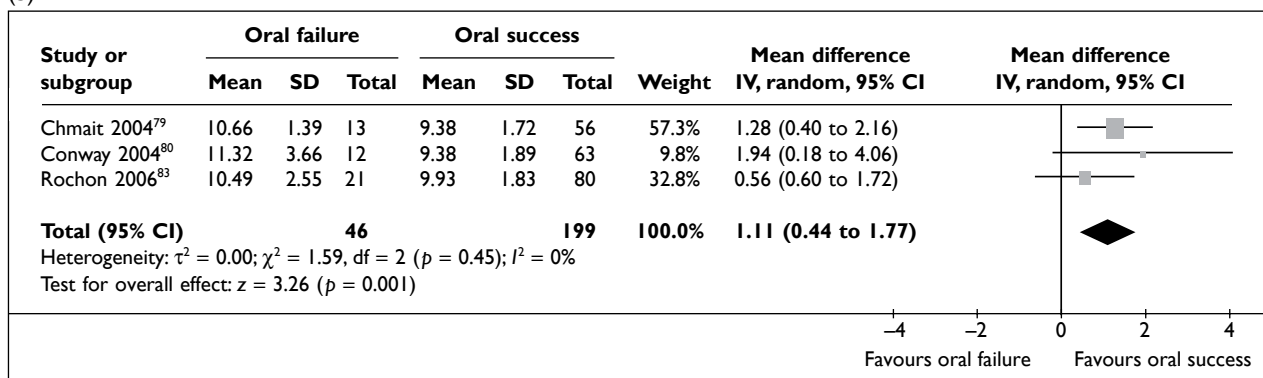


FIGURE 43 FBG (mmol/l) in OGTT as predictor of glibenclamide failure.

(a)



(b)



(c)

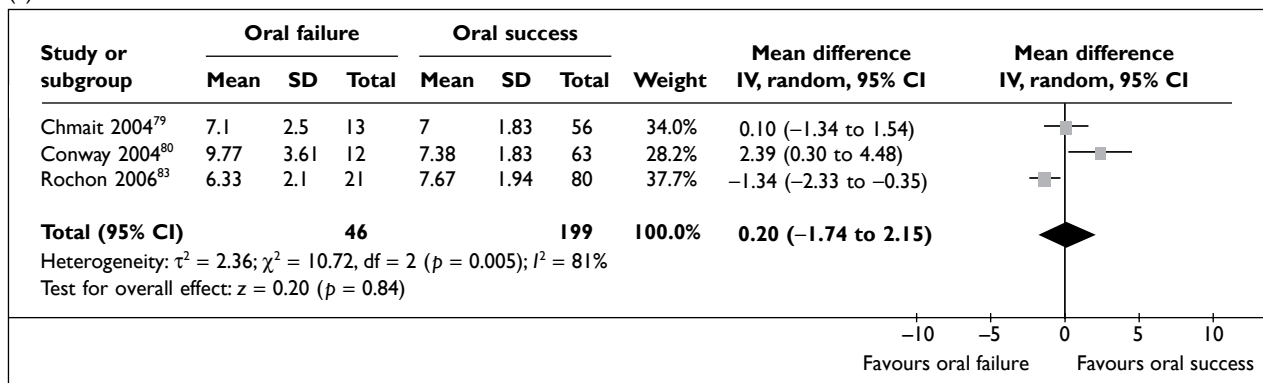


FIGURE 44 OGTT results: oral failure versus oral success. (a) 1-hour BG (mmol/l); (b) 2-hour BG (mmol/l); (c) 3-hour BG (mmol/l).

During treatment, both FBG and 1-hour post-prandial value were significantly lower in the glibenclamide success than in the failure group (FBG: 4.9 ± 0.6 mmol/l vs 6.3 ± 0.9 mmol/l, $p < 0.001$; 1-hour PPG: 6.9 ± 0.7 mmol/l vs 8.0 ± 1.1 mmol/l, $p < 0.001$). Results of the receiver-operator curve (ROC) analysis gave the following predictors for glibenclamide success: (1) dietary therapy failure after 30 weeks' gestation, and (2) dietary therapy failure at less than 30 weeks' gestation with mean FBG ≤ 6.1 mmol/l (110 mg/dl) and mean 1-hour PPG ≤ 7.8 mmol/l (140 mg/dl), with a sensitivity of 98% and a specificity of 65%.

Conway (2004)⁸⁰ found no clear cut-off levels in fasting glucose levels on the 3-hour OGTT for predicting glibenclamide failure. At FBG values of 5.3 mmol/l or more, 92% of women converting to insulin were detected, but with a false-positive rate of 70%. At 5.8 and 6.1 mmol/l, sensitivities were 67% and 50%, and false-positive rates were 40% and 29%, respectively.

Ethnicity

Rowan (2008)⁸⁸ found that there was a significant difference in ethnicity between those with adequate glycaemic control on metformin alone and those

requiring supplementary insulin, with significantly fewer Polynesians (11.8% vs 29.8%, $p < 0.001$) and significantly more Chinese/south-east Asians (16.9% vs 9.5%, $p = 0.04$) among those managing on metformin alone. Significantly more women in the group receiving supplementary insulin had had three or more terminations or miscarriages (33.9% vs 13.8%, $p < 0.001$), presumably because such a history was an indication for tight control. Langer (2006)⁸¹ also found a significant difference in ethnicity between women failing glibenclamide and women with adequate control on glibenclamide ($p = 0.00001$, no further details given).

Medication dose

In the study by Langer (2006),⁸¹ glibenclamide dose (more or less than 10 mg/dl) was also a significant variable in predicting glibenclamide success or failure ($p = 0.00002$, no further details given).

Maternal and neonatal outcomes

Most studies on glibenclamide success or failure found no significant difference in maternal or neonatal outcomes between the success and the failure groups (see above).

In contrast, Rochon (2006)⁸³ found a significantly higher NICU admission rate in infants of mothers in the glibenclamide success group than in the failure group. In a regression analysis they found that glibenclamide was predictive of NICU admission without other potential risk factors (including maximum dose used and length of glibenclamide use) playing a role. Of the studies of glibenclamide versus insulin, Holt (2008)⁵² reported no apparent difference in birth outcomes between women failing glibenclamide in their study and those who did not. Similarly, Rowan (2008)⁸⁸ reported no significant difference in their primary outcome composite and any of its components (neonatal hypoglycaemia, respiratory distress, phototherapy, birth trauma, Apgar score < 7 at 5 minutes, prematurity) when comparing women on metformin requiring supplementary insulin with those who did not.

Discussion

Our analysis of primary studies comparing oral treatment for hyperglycaemia in pregnancy with insulin included seven RCTs (published in full) and 20 cohort studies (nine published as abstracts), with a total of 4425 participants.

About two-thirds of participants were in studies comparing glibenclamide and insulin, about one-third was in trials comparing metformin and insulin, and a small trial had an acarbose group. Many of the studies were underpowered, as shown by the wide CIs in the forest plots, and had important quality deficits. Some data were available for most outcome measures we pre-specified, except for maternal depression, anxiety and health status. Only one trial reported follow-up data beyond delivery.

Glibenclamide versus insulin

Three RCTs reported on maternal hypoglycaemia for glibenclamide versus insulin. The largest trial (Langer 2000⁶⁸), with 404 participants, reported a risk ratio of 0.10 (95% CI 0.04 to 0.27), $p < 0.00001$, in favour of glibenclamide. The other two were small trials (Anjalakshi 2007⁶⁶ and Bertini 2005⁶⁷) (23 and 51 women respectively) and no maternal hypoglycaemic events were reported in either group. The two cohort studies reporting on maternal hypoglycaemia (Jacobson 2005⁷⁵ and Yogev 2004⁷⁸) both reported a significant difference, but in opposite directions.

There was a significant overall effect favouring insulin over glibenclamide for neonatal hypoglycaemia [risk ratio 2.07 (95% CI 1.04 to 4.11), $p = 0.04$], and birthweight [mean difference 89.6 g (95% CI -1.48 to 180.75), $p = 0.05$].

The cohort studies comparing glibenclamide and insulin showed no overall significant effect for any outcome except maternal FPG, where one cohort study (Jacobson 2005⁷⁵) favoured glibenclamide [mean difference -0.41 mmol/l (95% CI -0.58 to -0.24), $p < 0.00001$], but the one RCT (Langer 2000⁶⁸) showed no significant difference.

Metformin versus insulin

One RCT reported on maternal weight gain, and showed a significantly greater increase with insulin than metformin ($p < 0.001$), therefore favouring metformin treatment. Of the two cohort studies reporting this outcome, one showed a significantly greater weight gain with insulin and the other showed no difference between groups.

RCT evidence significantly favoured insulin treatment for the outcomes of preterm delivery and gestational age at delivery. Preterm delivery was higher with metformin than with insulin (12.1% vs 7.6%, $p = 0.04$), and gestational age at delivery showed a mean difference of -0.21 weeks

(95% CI -0.40 to -0.02, $p = 0.03$) with metformin. The observational studies for both outcomes showed no significant difference between treatments.

The two cohort studies reporting on neonatal hypoglycaemia showed a combined risk ratio of 0.60 (0.37 to 0.95), $p = 0.03$, favouring metformin. However, the two RCTs showed no significant difference for this outcome.

Acarbose versus insulin

The one acarbose versus insulin study, a small RCT (Bertini 2005⁶⁷), showed no significant difference between the groups on any of the 12 outcomes reported.

Other outcomes

None of the other outcomes showed an overall significant difference between groups in either RCTs or observational studies when comparing insulin with any oral agent.

In brief, we found no overall significant difference between oral treatment and insulin for the following outcomes (with the numbers in brackets denoting the total number of RCTs and observational studies respectively): rates of pre-eclampsia (3, 6), caesarean delivery (6, 8), maternal 2-hour PG (1, 1), maternal mean BG (1, 1), maternal HbA_{1c} (2, 0), induction of labour (3, 1), macrosomia (2, 8), LGA (3, 6), perinatal mortality (4, 6), birth trauma (3, 5), hyperbilirubinaemia (3, 4), need for phototherapy (2, 6), SGA (2, 5), NICU admission (3, 8), congenital malformations (3, 6), respiratory distress (3, 5) and 1-minute Apgar score (1, 4).

Preferences

The pregnant women appeared to prefer oral treatment to insulin treatment. Some gastrointestinal side effects were seen with metformin but none of the trials reported more serious adverse events.

Failure of oral drugs

Between 4% and 24% of women receiving glibenclamide switched to insulin because of inadequate control. Except in one study where none of the women failed metformin treatment, between 11% and 46% of women on metformin required additional insulin because of inadequate glycaemic control. In a direct comparison of glibenclamide and metformin, more participants failed metformin therapy than glibenclamide therapy (41% vs 20%, $p = 0.01$).

Eight observational studies reported data on predictors of failure on glibenclamide. Factors significantly associated with failure of glibenclamide treatment were earlier gestational age of diagnosis of GDM, higher levels of FBG, 1-hour BG, 2-hour BG, and a glibenclamide dose of < 10 mg/dl.

Factors that were not significant predictors of glibenclamide success or failure were maternal age, parity, maternal BMI, history of gestational diabetes and difference in maternal or neonatal outcomes.

Only one study, the RCT by Rowan (2008),⁸⁸ reported on predictors of failure on metformin. Factors significantly associated with requiring supplemental insulin were higher parity, higher maternal BMI, having three or more miscarriages, history of gestational diabetes, a maternal family history of diabetes, higher fasting glucose levels at enrolment and after OGTT, HbA_{1c} at enrolment and ethnicity.

Metformin versus glibenclamide

One RCT published in abstract form only found no significant difference for most maternal or neonatal outcomes after treatment with glibenclamide compared with metformin treatment; however, significantly more non-elective caesarean sections occurred in the metformin group (17% vs 3%, $p = 0.02$).

RCTs versus observational studies

Except for the cases indicated, no consistent differences were found between the results of the RCTs and the results of the cohort studies.

Adherence

There seems to be a presumption (as indicated unreferenced in the introductions of a range of studies) that oral medication may increase treatment adherence in women with gestational diabetes compared with insulin injections. However, none of the glibenclamide studies evaluated treatment adherence and the study of metformin versus insulin by Rowan (2008)⁸⁸ showed a *decreased* adherence with metformin. Moreover, only a small number of studies reported on glycaemic control so that it could not be checked systematically whether any differences seen in outcomes might be merely due to differences in glycaemic control or – in the absence of differences in glycaemic control – might be effects of the medication itself (or some other factor).

Limitations of our findings include:

- For most studies, study quality was limited and studies were underpowered (there were only three studies with 200 or more participants).
- Maternal outcomes tended to be neglected in comparison with neonatal outcomes.
- Especially, information on maternal glycaemic control during treatment was very limited; only one study reported using continuous glucose monitoring.
- Apart from a few cohort studies specifically studying this issue and from one RCT, information on glycaemic control with oral treatment and characteristics of those failing oral treatment was limited; also, hardly any information was available on glycaemic control with insulin (limited data suggest that in some studies control was not better, or may even have been worse, than that with oral treatment).
- Data on maternal quality of life, depression and anxiety are lacking.
- Data on perinatal mortality are of limited use as the studies were generally underpowered for assessing this outcome.

Conclusions

The review suggests that both glibenclamide and metformin can be used as alternatives to insulin, when diet and physical activity fail, in the treatment of hyperglycaemia in pregnancy. As neither drug has been licensed for use during pregnancy, women being offered treatment with these agents should be made aware of this and appropriately counselled. However there is, not surprisingly, some evidence that women prefer oral agents.

The RCT evidence showed little difference in results between the drugs and insulin. When comparing glibenclamide and insulin, there was

less maternal hypoglycaemia with glibenclamide, but less neonatal hypoglycaemia and lower birthweight with insulin. When comparing metformin with insulin, there was less maternal weight gain with metformin, but age at delivery favoured insulin.

With respect to identifying women at risk of failing to achieve adequate glycaemic control on oral agents, our review found an increased risk of glibenclamide failure with earlier gestational age of diagnosis of GDM, higher levels of BG (fasting or post-prandial), and a dose of < 10 mg/dl. Predictors of failure with metformin included higher parity, higher maternal BMI, having three or more miscarriages, a history of gestational diabetes, a maternal family history of diabetes, higher fasting glucose levels at enrolment and after OGTT, HbA_{1c} at enrolment, and ethnicity.

However, the current evidence base is not sufficient to allow the reliable identification at the time of diagnosis of women, or at diet failure, who will fail on oral therapy.

A trial comparing glibenclamide and metformin found that failure to achieve glycaemic control was more common among women receiving metformin (Moore 2008,⁹⁶ 41% vs 20%). However, it appears that insulin therapy is not a guarantee of achieving adequate glycaemic control. Within those studies that measured glucose levels among women receiving insulin, a significant proportion were found to have suboptimal glycaemic control.

In practice, the decision is not so much whether to use an oral drug or insulin, but when. If lifestyle measures fail, the next step could be to try an oral drug, with close monitoring to see if this is sufficient. If adequate control is not quickly obtained, a switch could be made to insulin.

Chapter 3

Screening

In this chapter, we examine selected studies which have appeared since the 2002 HTA report.³ These were selected from comprehensive searches, on the grounds that they might have new information. Many of the new studies found did not add anything to those in the previous review.

Many of the studies compare screening tests such as the FPG or the 50-g GCT against the 'gold standard' of the OGTT. That causes a number of problems:

- It is not really a gold standard.
- There are different OGTTs and criteria. Our default position is to use the 75-g OGTT.
- But most of all, this approach is 'pre-HAPO' and what we need now is to assess tests in the 'continuum age'. We are no longer looking to divide women into those who have or do not have gestational diabetes, but to quantify risk.

Before considering screening, we need to know:

- The glucose threshold at which intervention is indicated. This could be expressed in terms of the seven HAPO categories.
- Which measure of glucose to use – fasting or post load, and, if post load, 1-hour or 2-hour.
- When to screen. It has traditionally been at 28 weeks, but with an increasing proportion of hyperglycaemia in pregnancy being now type 2, there is a case for screening at booking clinic in first trimester. HbA_{1c} done then would pick up pre-gestational T2DM (if HbA_{1c} 6.5% or over), but could it also, at lower levels (say over 5.5%) detect pre-gestational hyperglycaemia which could be followed up with a post-load test such as the 50-g GCT or an OGTT?

(It might also be argued that if we are to tackle the problem at source – see Chapter 5, Discussion – that women with risk factors should be encouraged to have screening when they start planning pregnancies. So screening could be at three points – pre-conception, booking clinic and at 24 weeks.)

There may now also be a problem with the word 'screening'. Screening is usually used to refer to a simple but imperfect test which distinguishes

between those who probably have the condition and those who probably don't, and which is followed by diagnostic testing in those who are screen-positive. However, if we use FPG for detecting hyperglycaemia, is that screening or diagnosis? As was noted in a *Diabetes* editorial, measurement of maternal glucose at a single point in pregnancy was very effective at predicting birth outcomes.⁹⁶ However, it is always safer to confirm borderline or raised PG by a second test, which might mean another FPG rather than on OGTT.

Could we rely on FPG alone for making decisions on treatment? In the HAPO study, it was as good an indicator as the other measures for most, but not all, outcomes – post-load PG was better for three of the secondary outcomes, but differences were very small.

The correlations between the FPG and the other measures were surprisingly low at 0.38 and 0.30. It would be useful to know how many of the HAPO women who were in categories 1–4 by FPG were in categories 5–7 by post-load levels. If none or very few, then FPG could be used as the sole test.

Screening studies linked to outcomes

One problem with screening studies is that they often compare the performance of a screening test with the OGTT, rather than with patient outcomes.

The US Preventive Services Task Force looked specifically for studies which related results of screening test to outcomes of pregnancy, rather than to other measures of glucose such as the OGTT. Only two were found.⁴⁴ One was that by Cheng *et al.* (2007)³⁹ using GCT data, already described in Chapter 1.

The other was by Dodd *et al.* (2007)⁴⁰ from Adelaide (but excluding women who took part in ACHOIS). Women were screened with the 50-g GCT, and those who had PG of 7.8 mmol/l or more, went on to have a 75-g OGTT. Those who were GCT-negative did not have OGTTs. Using the

GCT and OGTT results, women were divided into groups:

- 1-hour GCT < 7.8, 7.8–11.0, and > 11.0 mmol/l
- FPG < 5.5, 5.5–7.0, and > 7.0 mmol/l
- 2-hour OGTT < 7.8, 7.8–11.0, and > 11.0 mmol/l.

Those with FPG of 7.0 mmol/l or over, or a 2-hour OGTT level of 11 mmol/l or more, were classed as having GDM and treated. Those in the intermediate group were diagnosed as having 'mild' GDM, and treated with diet, BG monitoring and insulin if necessary. This complicates interpretation, but some adverse outcomes increased in line with glucose levels despite treatment.

As with the HAPO study, Dodd *et al.* (2007)⁴⁰ found that:

'Our study indicates a continuum of adverse pregnancy outcomes with increasing levels of glucose intolerance. Using the information presented in the ROC curves, there does not appear to be a plasma glucose concentration above which the risk of adverse outcomes increases.'

Problem: relative risks and absolute numbers

A common finding in public health is that most events happen in people at low risk, because there are more of them. This is seen in the HAPO study.¹⁹

It could be argued that the 'purest' of the HAPO primary outcomes was cord blood C-peptide. Some would justifiably argue that it is just a biochemical measurement, not an outcome which matters to

patients, but of the others, macrosomia is a mixture of normal and abnormal big babies, delivery by section reflects clinical practice (range 8.6–23.5%), and neonatal hypoglycaemia may be affected by recording practice (range 0.3–6.4%). However, cord blood C-peptide was presumably a strong indicator of adverse outcomes.

The C-peptide results can be expressed in different ways as shown in *Table 16*, using FPG as the glucose measure.

So most of the adverse outcomes are in the low risk groups, with almost 60% being in the three lowest risk groups.

Let us assume that intervention could reduce adverse outcomes by half (a conservative assumption, if we look at ACHOIS¹⁸). Some exploratory calculations are shown in *Table 17*. Column 2 of the table shows the proportion of adverse outcomes which would be in each HAPO category, if reduced by half. So 12% of all such outcomes would be in category 2, and so on. Column 3 shows the proportion of the outcomes avoided by category. Over half of all the gains would be in categories 2 and 3. This is because their risks may be low, but their numbers are high. Column 4 shows the numbers needed to treat to avoid one adverse outcome, which is inversely related to the risk of outcomes.

However, the number needed to treat would be much greater in the lower categories, and hence the cost per adverse event avoided would be higher, as column 5 shows – it would cost 8.3 times as much to avoid an event in category 1 as in category 7. Expressed differently, if it cost £100 to prevent an adverse event, and we had £1000, we could prevent 10 events in category 7 or one in category 1.

TABLE 16 HAPO study: C-peptide above 90th percentile versus FPG categories

| HAPO glucose category | Relative risk | % of group with outcome | % of all women in HAPO with the outcome | Cumulative % of outcome |
|-----------------------|---------------|-------------------------|---|-------------------------|
| 1 | 1.0 | 4 | 8 | 8 |
| 2 | 1.41 | 6 | 24 | 32 |
| 3 | 1.75 | 8 | 27 | 59 |
| 4 | 2.36 | 12 | 17 | 76 |
| 5 | 3.62 | 11 | 12 | 88 |
| 6 | 4.46 | 23 | 8 | 96 |
| 7 | 7.65 | 32 | 4 | 100 |
| All | | | 100 | |

TABLE 17 Exploratory calculations: if treatment were to reduce HAPO outcomes by half

| HAPO category | % of all outcomes if treatment reduced outcome by half | % of absolute gain from each category | NNT to avoid one adverse outcome | Cost ratio with category 7 as reference |
|---------------|--|---------------------------------------|----------------------------------|---|
| 1 | 4 | 8 | 50 | 8.3 |
| 2 | 12 | 24 | 33 | 5.5 |
| 3 | 13.5 | 27 | 25 | 4.2 |
| 4 | 8.5 | 17 | 17 | 3.0 |
| 5 | 6 | 12 | 18 | 3.0 |
| 6 | 4 | 8 | 9 | 1.5 |
| 7 | 2 | 4 | 6 | 1.0 |

Note that treatment is not the only cost. It is much more cost-effective to treat women in category 7, but it is much more expensive per each case identified. Using the numbers in the C-peptide column in *Table 2* (HAPO glycaemia categories), we would need to screen 107 women to find each one in category 7, compared with only 4 in category 3. However, that assumes universal screening, and the cost of finding the category 7 women would be reduced by selective screening – though not all might be found. This issue is dealt with in Chapter 4.

Implication: if we are only going to treat women at higher risk, we need to define how high that risk has to be, and consider the most efficient screening strategies for detecting those women. For example, if we were only going to treat HAPO categories 6 and 7, we need to know how many of those women would be identified by different degrees of selectivity of screening, for example if only women with BMI over 30 had glucose measured. The HAPO study has not yet published data on the age and BMI predictors of the higher glucose categories.

Choice of test

As mentioned in Chapter 1, Agarwal and Dhath (2007)¹¹ reviewed the variation in diagnostic criteria. They also considered choice of test. They were not impressed by the OGTT:

‘It is expensive and time-consuming. It is non-physiologic, unpleasant, not reproducible, unrelated to body weight, and its predictive value may vary with ethnic origins.’

However they noted that it was still the diagnostic test recommended by the expert panels, despite

the lack of agreement on the glucose load (75 g vs 100 g – they could also have mentioned 50 g being used in Australia), as well as on cut-offs.

Fasting plasma glucose

Agarwal and Dhath (2007)¹¹ have produced several papers examining the value of FPG as the screening test. They note¹¹ its benefits – easy to administer, well tolerated, inexpensive, reliable and reproducible. They noted that some studies of FPG had selection biases, such as trialling FPG only in those who have been screen positive after a 50-g GCT.

They note that the value of FPG screening varies according to the diagnostic criteria used – good with the ADA, poor with WHO. They make a useful suggestion that if the OGTT is to be used as the one-step screening test in high risk populations, swift reporting of a high FPG, or of a fasting capillary glucose (FCG)⁹⁸ would avoid the need for the rest of the OGTT. When comparing different FCG thresholds against the full OGTT results, they concluded that an FCG level of under 4.7 mmol/l could be used to rule out GDM, and one of 6.1 mmol/l or more to rule in the diagnosis, thereby reducing the number of OGTTs required by half.

In a low risk Swedish population, Fadl *et al.* (2006)⁹⁹ showed that an FPG of 4 mmol/l or over had high sensitivity for GDM + IGT [2-hour capillary glucose (CG) over 9 mmol/l]. But specificity was poor at 51%.

HbA_{1c}

The last HTA report³ dismissed HbA_{1c} as a screening option on the grounds of insensitivity. Improvements in measurement of HbA_{1c} have made it a more reliable and standardised test and

it is now recommended by an expert committee for diagnosing non-gestational T2DM.¹⁰⁰ However, the timescale of changes in HbA_{1c} make it unlikely that it would be rendered abnormal by PG rising over a few weeks. There have been a few studies in recent years. Agarwal *et al.* (2005)¹⁰¹ measured HbA_{1c} at the same time as 75-g OGTTs at 24–28 weeks in 442 women in the United Arab Emirates, a high risk population. They found complete overlap of HbA_{1c} results in women with and without GDM. No level of HbA_{1c} could be used as a cut-off to rule out GDM. Agarwal *et al.* (2005)¹⁰¹ also review other studies, which nearly all reported that HbA_{1c} was not useful.

HbA_{1c} can therefore be dismissed again as a third trimester screening test. That does not mean that it may not have a role in earlier screening at booking clinic, where it might have a role in identifying women with pre-gestational hyperglycaemia (either T2DM or non-diabetic hyperglycaemia). Research is needed in that situation. Aldasouqi and Gossain (2009)¹⁰² suggest that using serial HbA_{1c} measurement at 4-weekly intervals starting around mid-pregnancy might reduce the numbers of women requiring OGTT.

Simplified oral glucose tolerance tests

Anderberg *et al.* (2007)¹⁰³ suggest using the 75-g OGTT but measuring only the 2-hour PG (but not measuring the FPG). That could make screening much more convenient for women. They used a cut-off of 9 mmol/l for diagnosing GDM, with those in the borderline group of 7.8–8.9 mmol/l having a repeat OGTT a week later. Unfortunately the paper does not say how many had different results between OGTTs.

Anjalakshi *et al.* (2007)⁶⁶ in Chennai, India, compared a 75-g GCT (non-fasting) with the standard OGTT and found no difference, implying that it matters not whether women have fasted or not.

Ayach *et al.* (2006)¹⁰⁴ report that the OGTT could be shortened for many women by using a 1-hour level of under 140 mg/dl (with the 100-g OGTT) to rule out GDM, with no testing at 2 or 3 hours.

It should be noted that these studies are based on the GDM/no GDM dichotomy.

Early screening

Screening for GDM has traditionally been done in around the start of the third trimester, at 24–28 weeks' gestation. The rationale is that insulin resistance is due to placental hormones (lactogen) which reach their highest level around then. Several commentators have raised concerns about leaving it so late. The American College of Obstetrics and Gynecology (ACOG) summed the problem up in its 2001 guidelines:¹⁰⁵

'Insulin resistance increases as pregnancy progresses, therefore, testing later in pregnancy will result in a higher yield of abnormal tests. However, the later the abnormality is diagnosed, the less time will be available for intervention.'

The ACOG guideline commented that the recommendation to screen at 24–28 weeks was an arbitrary decision.

Riskin-Mashiah *et al.* (2009)¹⁰⁶ point out that the standard two-stage process of screening and diagnostic testing takes time away from the brief therapeutic window for treatment. They suggest that this may be one reason why intervention has often failed to have much effect on outcomes – it is coming too late. They cite the study by Schaefer-Graf *et al.* (2003)¹⁰⁷ which reported that 20% of fetuses showed macrosomia on ultrasound at diagnosis of GDM. Riskin-Mashiah *et al.* (2009)¹⁰⁶ argue that the optimum time for lifestyle intervention might be at the end of the first trimester, after morning sickness has abated and when renewed appetite may lead to excessive weight gain and an increased risk of GDM.

Riskin-Mashiah *et al.* (2009)¹⁰⁶ carried out a retrospective study of 6129 sets of case notes of women delivered over a 5-year period and who had a first trimester FPG level recorded, the mean gestation at time of FPG being 9.5 weeks.¹⁰⁶ They divided FPG into seven bands similar to HAPO, and compared rates of development of GDM, LGA, macrosomia and caesarean section. Their results are shown in *Table 18*.

Hence, the frequency of later GDM is low until after band 4. However, the relationship between first trimester FPG and LGA/macrosomia is more linear, as is the frequency of caesarean section.

One weakness of this study for our purposes is that there were no post-natal data on maternal glycaemic status. Some of those with early hyperglycaemia might have had pre-gestational T2DM rather than GDM. However, the study supports the HAPO findings of a continuum of risk.

Bartha *et al.* (2000)¹⁰⁸ in Spain screened 3986 women at the first antenatal visit, using a 50-g GCT and following up levels over 140 mg/dl with a 100-g OGTT. They then divided women who developed GDM into two groups, early diagnosis (mean 18 weeks gestation) and late (mean 33 weeks). In practice the late group were those whose early tests had been normal but who were diagnosed after being re-screened at 24–28 weeks. (NB the delay to diagnosis at 33 weeks supports the concern of Riskin-Mashia *et al.* (2009)¹⁰⁶ about missing the key period for intervention.)

Bartha *et al.* (2000)¹⁰⁸ reported that 5.9% of women had GDM, of whom 28% were in the early diagnosis group. This group had higher pre-gestational BMI than the late diagnosis group – 29 versus 25. No data on post-natal glucose levels are given, so again it is possible that some of the early diagnosis group had T2DM before pregnancy. They were more likely to require insulin (34% vs 7% for the late onset group) and to have had a history of hypertension (19% vs 6%).

Most *et al.* (2009)¹⁰⁹ carried out a 50-g GCT at first visit (mean gestation not given: stated to be first trimester, and to be prior to 16 weeks) and in those who were negative, again at 24–28 weeks. Of 340 women diagnosed with GDM (100-g OGTT), 29% were diagnosed after their first visit. The early

diagnosis group were older (34 years vs 30 years) and heavier (BMI 28 vs 26: percentages with BMI < 25, 24% and 50%). Women with early diagnosis of GDM were more likely to require drug treatment than the late onset group (45% vs 19%). Once again, no post-natal glucose data were given, so some of the early diagnosis group may have had pre-gestational diabetes.

Seshiah *et al.* (2008)¹¹⁰ compared glycaemic indicators and outcomes in women diagnosed at different gestational ages. All had 75-g OGTTs and HbA_{1c}. However, it is not clear whether those diagnosed later in pregnancy had been screen-negative earlier. They were a group at higher than usual risk, as shown by their eventual cumulative prevalence of GDM of 42%, compared with the host population's 17%. The study was based in Chennai, India. Women known to have had pre-gestational diabetes were excluded.

Seshiah *et al.* (2008)¹¹⁰ divided the women into five groups, the first four being based on gestational age at diagnosis of GDM, and the fifth being women who had normal glucose tolerance. The WHO criterion used for the diagnosis was 2-hour PG 140 mg/dl or over. Their bands and other details are shown in *Table 19*.

The HbA_{1c} was done at the same time as the OGTT. The high HbA_{1c} in group 1 suggests that these women had had undiagnosed T2DM before pregnancy.

The birthweight figures suggest that early diagnosis may allow more effective intervention. Sixty-two percent were diagnosed before 24 weeks of gestation, but it should be remembered that this

TABLE 18 Outcomes by band of first trimester FPG: Riskin-Mashiah *et al.* (2009)¹⁰⁶

| Band of FPG | % of women | % who developed GDM | Odds ratio for GDM | % with LGA or macrosomia | Odds ratio for LGA or macrosomia |
|---------------------------|------------|---------------------|--------------------|--------------------------|----------------------------------|
| 1. <75 mg (<4.2 mmol) | 25 | 1 | 1.0 | 7.9 | 1.0 |
| 2. 75–79 (4.2–4.43 mmol) | 26 | 2 | 2.0 | 8.4 | 1.1 |
| 3. 80–84 (4.4–4.6 mmol) | 23 | 2.4 | 2.4 | 11.8 | 1.6 |
| 4. 85–89 (4.7–4.9 mmol) | 15 | 3 | 3.0 | 11.2 | 1.5 |
| 5. 90–94 (5–5.2 mmol) | 7 | 9.4 | 9.3 | 14.7 | 2.0 |
| 6. 95–99 (5.3–5.5 mmol) | 3 | 8.4 | 8.6 | 17.3 | 2.5 |
| 7. 100–105 (5.6–5.8 mmol) | 2 | 11.7 | 11.9 | 19.4 | 2.8 |

Conversions to mmol/l are rounded.
Values are mean ± SD unless indicated otherwise.

was a high risk group. However, perhaps high risk women should be screened earlier in pregnancy. The slight rise in HbA_{1c} from groups 2 to 4, might suggest that the later onset group could have been hyperglycaemic for longer.

Could HbA_{1c} be used as a screening test? There is a clear difference between all the GDM groups, but confidence intervals are wide. Or could an early HbA_{1c} at time of booking be used for triage of women into four groups:

- 6.5% or over – assume diabetes
- 6.0% to 6.4% – treat as HGP
- under 5.3% – assume that HGP can be ruled out, with no further testing
- 5.4 to 5.9% – re-test in 3rd trimester?

Agarwal and Dhath (2007)¹¹ report that glucose screening in early pregnancy can detect most cases of GDM, but that FPG is not suitable, since in the early stages, as with T2DM, hyperglycaemia is only post prandial. Hence the 50-g GCT is recommended, at least in high risk populations.

Sacks *et al.* (2003)¹¹¹ also investigated the value of an early (mean 10 weeks' duration) FPG and concluded that it was an unsatisfactory test because of poor specificity.

Selective or universal screening

NICE recommended selective screening based on the ADA criteria, or on high risk ethnicity.² This recommendation was based on the probability of being diagnosed with GDM on the basis of the 75-g OGTT, and so belongs to the dichotomy era.

What we need to know now is the intervention threshold, in terms of HAPO category, and how good selection criteria are in terms of negative

predictive value. If we used, say, both age under 25 years and BMI under 28 as exclusion criteria from selective screening, how many women in HAPO categories 5–7 would be missed? The HAPO study¹⁹ has the data but this analysis has not yet been carried out.

The 2002 HTA report³ concluded that selective screening by risk factors would miss about half of the women with GDM. A recent before and after study from Paris, Cosson *et al.* (2006),¹¹² comparing selective versus universal screening, reported that GDM was diagnosed in 8.3% and 12.6% respectively. An odd feature in this study was that outcomes were as good as, and sometimes slightly better, in those women with GDM found by universal screening than in non-diabetic controls. In addition to treatment to control glucose levels, they also had enhanced monitoring of blood pressure, weight, proteinuria and fetal heart rates.

This is reminiscent of the ACHOIS trial,¹⁹ where the intervention group did better than the non-diabetic population norm, suggesting that the improvement may be due to more than just glucose control, but may, as pointed out by Masson and Lindow (2006),¹¹³ reflect provision of a more comprehensive package of care.

Conclusions

Most studies published since the previous HTA review³ have compared a number of screening tests with the presence or not of GDM (variably defined) based on the OGTT (various forms). These are not that applicable in the post-HAPO era, where the key questions are:

1. At what level of PG is intervention worthwhile? This could be expressed in terms of the HAPO categories.
2. What measure of PG should we use?

TABLE 19 Bands by gestational age at diagnosis: HbA_{1c} and birthweight – from Seshiah *et al.* (2008)¹¹⁰

| | Gestational age at diagnosis | HbA _{1c} (figures in brackets as provided by authors – presumably SD but not stated) | Birthweight (kg) |
|---------|------------------------------|---|------------------|
| Group 1 | < 12 | 6.9% (1.62) | 3.15 |
| Group 2 | 13–23 | 6.0% (0.79) | 3.09 |
| Group 3 | 24–30 | 6.1% (0.93) | 3.32 |
| Group 4 | > 30 | 6.2% (0.31) | 3.51 |
| No GDM | | 5.3% (0.43) | 3.28 |

3. Can de-selection by absence of risk factors remove many women from BG testing?

FPG is looking as if it might suffice, thereby avoiding the costs and inconvenience of the OGTT. However, we still need to know what proportion of adverse events occurred in HAPO in those who were in categories 1–4 by FPG but in higher categories by post-load PG.

Question 3 could also be answered by further analysis of the HAPO data.

So this is not so much a case of saying that ‘more research is necessary’ but of recommending further analysis of data already collected, which could be done over a much shorter timescale.

Chapter 4

Review of cost and cost-effectiveness studies

Methods

Search strategy

The databases MEDLINE, EMBASE, Web of Science with Conference Proceedings, and Centre for Reviews and Dissemination (CRD) databases were searched for the years 1996–June 2009. The results of the searches were screened by two authors and then checked by a third author for inclusion. Full details of the search strategies are shown in Appendix 1.

Terminology

A number of papers have reported mg/dl. These have been converted to mmol/l by dividing by 18 with results presented to one decimal place.

Price indexing and foreign currency conversions

Within this literature review, a base year of 2008 has been applied for costs and prices with sums converted being reported in square brackets: [£XX]. Where papers used an alternative base year, the Hospital and Community Health Services Index, as reported within the Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care, has been applied.¹¹⁴ Where costs and prices were reported in a foreign currency these were converted to pounds sterling using the exchange rate prevailing on 5 April at the end of the base year of the paper, the Hospital and Community Health Services Index being subsequently applied to the resultant pounds sterling amount if required. Where the base year was not stated within the paper it was assumed to be the publication year.

Treatment of gestational diabetes: cost studies

Chen *et al.* (2009)¹¹⁵ in a relatively complicated comparative analysis of National Hospital Discharge Survey statistics in the USA, estimated the additional cost arising from pregnancy management among women with gestational

diabetes as compared with women without gestational diabetes in 2007 US\$. (Note that the 5 April 2007 exchange rate was US\$1.97/£1, which could be seen as historically unrepresentative and unduly high. Similar concerns may apply elsewhere in this review to 5 April 2008 when the exchange rate was US\$1.99/£1.) In the USA in 2007, the authors estimated that the prevalence of gestational diabetes ranged from 1.3% in those under 20 years to 8.7% in those over 36 years, with a national average prevalence of 4.5% amounting to an annual 180,000 pregnancies with gestational diabetes.

Mothers with gestational diabetes used more inpatient days than those without gestational diabetes, with ratios of days (estimated through poisson regression) for caesareans (1.195); pre-eclampsia (1.499); other hypertension complication (1.560); and, 'other pregnancy-related event' (1.286), all statistically significant. They used about half the days for amniotic cavity infections. Ratios of rates for emergency visits where pregnancy was within the secondary diagnosis code (1.426) were also significant. With regards to 'other ambulatory visits' these were typically also significant, with ratios of rates for caesareans (presumably for post-operative follow-up) (1.221); polyhydramnios (1.855); urinary tract infection (1.119); pre-eclampsia (1.454); other hypertension complication (1.495); 'other pregnancy-related event' (1.386); and visits where pregnancy was within the secondary diagnosis code (1.123).

Ratios of rates of inpatient days among newborns to mothers who had gestational diabetes compared with those of non-gestational diabetes were significant for hospital inpatient days for: endocrine and metabolic disorders (2.907); respiratory distress syndrome (0.701); jaundice (1.754); congenital abnormalities (0.676) and 'other neonatal events' (1.035). Emergency visits rates were not statistically significantly different. Ratios of rates for 'other ambulatory visits' were significant for: macrosomia (1.826); endocrine and metabolic disorders (3.443); birth trauma (0.620); other complications of labour (1.315); respiratory distress syndrome (0.820); jaundice (1.213);

congenital abnormalities (1.127); and 'other neonatal events' (1.027).

Given these rates and the prevalences of gestational diabetes across the age spectrum, the authors estimated an average additional cost per mother with gestational diabetes of US\$3305 [£1733] and an average additional cost per newborn to a mother with gestational diabetes of US\$209 [£110]. So an increasing prevalence of gestational diabetes will place a considerable cost burden on health services.

Cost of different treatments

Todorova *et al.* (2007)¹¹⁶ undertook a prospective study among 50 Bulgarian women diagnosed with gestational diabetes between weeks 18 and 28 using the 75-g OGTT. Patients were allocated to either treatment through diet alone ($n = 30$) or through diet and insulin ($n = 20$) at diagnosis, though among the diet group if pre-prandial blood sugar levels exceeded 6.0 mmol/l, or 2-hour post-prandial levels exceeded 7.5 mmol/l, or HbA_{1c} rose above 6.5%, insulin treatment would be added. The method of allocation of patients to groups was not specified. Outcomes measured included macrosomia, pre-eclampsia, concomitant infections, caesareans, normal births and birthweight.

The baseline pre-prandial and post-prandial BG measurements were significantly higher among the insulin group than the diet group, suggesting that patient allocation between groups may have been clinically determined. Despite this, after treatment blood sugar levels in the insulin group improved while those in the diet group worsened to the extent that BG measurements were significantly lower among the insulin group than among the diet group. None of the outcome measures were statistically significantly different between the two groups.

In terms of cost the authors found an average cost without complications for the diet group of Lv453 [£169] as compared with Lv470 [£175] for the insulin group, which was statistically significant. The net cost of Lv16.70 [£6.20] was attributable to insulin and the associated consumables. The with-complications average cost was Lv492 [£184] in the diet group and Lv540 [£202] in the insulin group. The authors performed a cost-effectiveness comparison based upon the cost of achieving glycaemic control but the method applied is unclear and the chosen outcome measure not

obviously relevant. The study is best seen as a costing study, though questions over the allocation of patients to the two treatment groups mean that it may be better viewed as a prospective costing study rather than a comparison of the costs of alternatives for a given patient group.

Goetzl and Wilkins (2002)¹¹⁷ undertook a decision tree analysis of the costs of glyburide therapy compared with insulin therapy for patients with gestational diabetes. Insulin therapy resulted in 20% of patients having a severe hypoglycaemic episode. Hospitalisations would occur for 1–2 days for 0.5% of severe hypoglycaemic episodes, with the remainder requiring outpatient treatment. Of those receiving glyburide 4% would not achieve adequate control and would be put on to insulin with the associated probabilities of severe hypoglycaemia, hospitalisation and outpatient treatment. For those achieving adequate control with glyburide, only 1.99% would have a severe hypoglycaemic episode. With the exception of the 0.5% hospitalisation rate for severe hypoglycaemic episodes, these effectiveness estimates were drawn from the Langer *et al.* (2000)⁶⁸ comparison of glyburide with insulin for gestational diabetes.

Given that glyburide had a lower weekly acquisition cost of US\$6.75 [£5.79] compared with US\$17.77 [£15.25], with insulin initiation costing US\$3.55 [£3.05] and transferring from glyburide to insulin US\$39.36 [£33.78] it would be anticipated that glyburide would be less costly than insulin. The average cost per inpatient stay was estimated as US\$1551 [£1331]. This resulted in an estimated cost saving from the use of glyburide of US\$166 [£142].

Ogunyemi *et al.* (2007)⁶⁹ reported that medication costs for the average doses used were US\$7/month for glibenclamide and US\$20/month for insulin (no further analysis).

Lai *et al.* (2008)¹¹⁸ performed a cost analysis of metformin versus insulin in gestational diabetes (published in abstract form), based on the data of the trial by Rowan (2008)⁸⁸ (46% of patients receiving metformin required additional insulin, increased preterm deliveries in the metformin group). Cost of insulin was calculated at an assumed quantity of 1000 U/month. Cost of metformin was calculated at all dose ranges from 500 mg to a maximum dose of 2500 mg per day. A model for estimating costs of preterm delivery was created. At a failure rate of 46%, metformin therapy was less costly than insulin therapy

(US\$335 vs US\$404); metformin therapy costs exceeded insulin therapy costs at a metformin failure rate of 76%. When additional costs of neonatal care for preterm delivery were taken into account, metformin therapy costs exceeded insulin therapy costs at a failure rate of 7%.

Kitzmilller *et al.* (1998)¹¹⁹ undertook a cost-consequence analysis of samples of patients diagnosed with gestational diabetes within the universal screening programme in North California ($n = 140$), New England ($n = 149$) and Southern California ($n = 66$) using the 1-hour 50-g OGCT with a 7.2-mmol/l cut-off, or 7.8 mmol/l if tested in the 1-hour fasting state as in Southern California. A positive screen was confirmed with the 3-hour 100-g OGTT.

Those diagnosed with gestational diabetes in North California were referred to the 'Sweet Success' programme, which through diet aimed to control FBG to below 5.5 mmol/l and 1-hour post-prandial BG to 7.2 mmol/l. If after 2 weeks more than 20% of BG results fell above target, patients were initiated on insulin therapy with one to three daily injections of human insulin, NPH and regular as needed. Those on insulin were also recommended to have fetal surveillance of weekly non-stress fetal heart rate monitoring after 35 weeks plus ultrasound at 38 weeks to rule out macrosomia.

Those diagnosed with gestational diabetes in New England underwent a similar programme of dietary advice, though with slightly different targets of FBG to below 5.6 mmol/l and 2-hour post-prandial BG to 6.7 mmol/l. Initiation of insulin followed a similar consideration as the North California programme. All those diagnosed with gestational diabetes received fetal surveillance along the lines of those diagnosed with gestational diabetes and requiring insulin within the North California programme.

Those diagnosed with gestational diabetes in Southern California with a FBG below 5.9 mmol/l were immediately given insulin therapy. The remainder of those diagnosed with gestational diabetes underwent a similar programme of dietary advice to the other programmes, but again with slightly different targets of FBG to below 5.9 mmol/l and 1-hour post-prandial BG to 7.8 mmol/l. Fetal surveillance included weekly non-stress fetal heart rate monitoring after 32 weeks, two to three ultrasounds to evaluate fetal growth and amniocentesis at 38 weeks if the cervix was favourable for induction. For reasons that are not

clear, the clinical outcomes reported in the paper for the Southern California sample were restricted to those receiving insulin, differentiated by glucose monitoring regime.

The authors also estimated the costs of diagnosis, the costs of outpatient treatment of gestational diabetes, the costs of inpatient treatment of gestational diabetes, the costs of delivery and the neonatal treatment costs within the US setting, based on reimbursement rates for the North California managed care market. This resulted in the following cost estimates, where input costs covered diagnosis and treatment of gestational diabetes, and output costs covered antepartum care, delivery and post-delivery care (as shown in *Table 20*).

As would be anticipated, the input costs for insulin users were consistently significantly higher than those controlling their gestational diabetes with diet alone. This discrepancy was greater in the North California sample than in the New England sample, as would again be anticipated given that only those on insulin in the North California sample received heightened fetal monitoring as compared with all those in the New England sample. Output costs were also higher on average among those receiving insulin. This was particularly evident within the New England sample, which might perhaps suggest that universal fetal monitoring helped control complications and costs within the diet subsample as well. However, perhaps more pertinent to note is that within the North California sample only 30% received insulin while in the New England group 55% received insulin.

The authors also provided some estimates of the incremental cost per outcome comparing the pre-prandial monitoring of BG and post-prandial monitoring of BG in the Southern California programme. This estimated that post-prandial BG monitoring had an additional input cost of US\$174 [£176] per patient but resulted in a total cost saving of US\$344 [£338]. The additional input cost of US\$174 [£176] was linked to only five caesarean sections being required in the post-prandial monitoring subsample as compared with 13 in the pre-prandial monitoring subsample to yield an estimated input cost per caesarean avoided of US\$34.80 [£35.23]. But whether such a marked difference in caesarean rates for post-prandial monitoring as compared with pre-prandial monitoring can be confidently predicted

TABLE 20 Cost estimates: Kitzmiller et al. (1998)¹⁹

| | n | Input | Output | Total |
|---|----------|------------------|----------------------|----------------------|
| Northern California | | | | |
| Diet | 98 | US\$817 [£825] | US\$5762 [£5820] | US\$6579 [£6645] |
| Insulin | 42 | US\$1838 [£1856] | US\$6462 [£6527] | US\$8300 [£8383] |
| All | 140 | US\$1123 [£1134] | US\$5993 [£6053] | US\$7116 [£7187] |
| New England | | | | |
| Diet | 67 | US\$882 [£891] | US\$6096 [£6157] | US\$6978 [£7048] |
| Insulin | 82 | US\$1425 [£1439] | US\$11,216 [£11,328] | US\$12,641 [£12,767] |
| All | 149 | US\$1180 [£1192] | US\$8914 [£9003] | US\$10,094 [£10,195] |
| Southern California (insulin differentiated by BG monitoring regime) | | | | |
| Pre-prandial | 33 | US\$3596 [£3632] | US\$8013 [£8093] | US\$11,609 [£11,725] |
| Post-prandial | 33 | US\$3770 [£3808] | US\$7495 [£7570] | US\$11,265 [£11,378] |
| All | 66 | US\$3673 [£3710] | US\$7754 [£7832] | US\$11,427 [£11,541] |

from this study given the subsample sizes of 33 is questionable.

Treatment of gestational diabetes: cost-effectiveness studies

Moss *et al.* (2007)¹²⁰ undertook a cost consequence analysis of the Australian ACHOIS trial,¹⁸ within which women diagnosed with mild gestational diabetes defined by a 75-g fasting OGTT result overnight of less than 7.8 mmol/l and after 2 hours between 7.8 mmol/l and 11 mmol/l were randomised to receive either dietary advice, BG monitoring and insulin if required ($n = 474$) or routine care ($n = 496$).

Costs were estimated from randomisation to discharge of the mother or baby, whichever occurred later. Direct costs were measured to the health system, as were direct charges to the patient and non-medical costs and opportunity costs to the patient and immediate family. Unit costs were derived from sources consistent with the Pharmaceutical Benefits Advisory Committee guidelines.

In the intervention group singleton pregnancies were significantly less likely to experience any serious perinatal outcome with 1.1 per 100 compared with 3.2 in the routine care group, an adjusted relative risk of 0.33. All serious perinatal outcomes in the intervention group were limited to shoulder dystocia ($n = 7$, 1.5%), and while

the majority in the routine care group were also shoulder dystocias ($n = 16$, 3.2%), a number of infants died ($n = 5$, 1.0%), had bone fracture ($n = 1$, 0.2%) and/or nerve palsy ($n = 3$, 0.6%) though none of these outcomes were individually statistically significant. But among the intervention group there was a significantly higher relative risk of being admitted to neonatal nursery of 68.1 per 100 compared with 59.5 and an adjusted relative risk of 1.15. Mothers in the intervention group were significantly more likely to have labour induced with 30.0 per 100 compared with 28.3 and a relative risk of 1.34, but there was no difference in caesareans which saw a non-significant relative risk of 0.97.

Mothers in the intervention group made 0.7 fewer antenatal clinic visits, but 2.5 more specialist medical clinic visits, 1.6 more dietician visits, 1.79 more diabetic educator visits and received insulin more often than the routine care group: relative risk 6.18. As a consequence the average direct outpatient costs were AU\$674 [£310] in the intervention group as compared with AU\$337 [£155] in the routine care group: a 100% increase of AU\$337 [£155]. The average inpatient costs were also higher in the intervention group at AU\$5451 [£2510] compared with AU\$5249 [£2417]: AU\$202 [£93] greater, though the authors noted that this was not statistically significant. This led to a total average cost to the health-care system of AU\$6126 [£2821] in the intervention group and AU\$5586 [£2572] in the routine care group: an increase of AU\$540 [£249].

Direct charges to the family as estimated through a questionnaire were also higher in the intervention group [$n = 52$], averaging US\$143 [£66] as compared with AU\$82 [£38] in the routine care group [$n = 56$], an increase of AU\$61 [£28] or AU\$65 [£30] if mother and partner time off paid work was included.

As a consequence, the authors estimated that cost per serious perinatal complication prevented was AU\$27,503 [£12,668], and, though not statistically significant in itself, the cost per perinatal death avoided was AU\$60,506 [£27,869], which if population-based life tables were applied with a discount rate of 5%, resulted in a cost per life-year of AU\$2988 [£1376]. So intervention was highly cost-effective, though it should be noted that screening and diagnostic costs were not included.

Screening for gestational diabetes: cost studies

Lavin *et al.* (2001)¹²¹ estimated the direct costs and patient time of the alternative screening strategies:

- a two-tiered strategy of the 1-hour 50-g OGCT with a 7.8-mmol/l cut-off followed by a confirmatory 3-hour 100-g OGTT among positive results
- a one-tiered strategy of the 2-hour 75-g OGTT.

The proportion of patients with a positive result from the 50-g GCT was taken from the literature, estimates ranging from 12.0% to 17.1%. The direct costs of the tests in the two-tiered strategy were estimated as between US\$2.60 [£2.23] and US\$5.56 [£4.77] for the GCT and between US\$7.16 [£6.14] and US\$13.54 [£11.62] for the 100-g OGTT, yielding an average cost per patient of between US\$3.46 [£2.97] and US\$7.88 [£6.76]. In comparison the one-tiered strategy averaged between US\$5.64 [£4.84] and US\$10.88 [£9.34] for the 75-g OGTT.

Assuming a patient time of 1 hour for the 50-g GCT and 3 hours for the 100-g OGTT resulted in an average patient time of 1.4 and 1.5 hours for the two-tiered strategy as compared with 2 hours for the one-tiered strategy. Travel time in addition to this was estimated as between 2.2 and 2.3 hours for the two-tiered test as compared with 2 hours for the one-tiered strategy, suggesting that testing time differences and travel time differences largely cancel out between the two strategies on average. But if the GCT could be administered in conjunction with a standard prenatal visit, the two-

tiered strategy appeared to involve less patient time than the one-tiered strategy.

On this basis the authors concluded that the two-tiered approach was likely to be both cheaper and more convenient, particularly in light of the 50-g GCT not requiring fasting. But the authors acknowledged that the study did not consider the sensitivity and specificity of the testing strategies, which could radically alter their total costs.

Moses *et al.* (1997)¹²² provided an estimate of the cost per test for gestational diabetes within the Australian context, together with estimates of the resource use that flowed from a positive diagnosis of gestational diabetes. The cost per test was AU\$9.55 [£7.62] for a single sample, those testing positive being given dietary advice, target ranges for daily dietary kilojoules, and BG monitoring strips, the home glucose meter being hired by the patient for AU\$10. Those missing the target of 90% of both FPG of less than 5.5 mmol/l and 1-hour PPG of less than 8.0 mmol/l received a twice-daily dose of premix insulin.

Among the 134 patients treated over a 1-year period in the area for gestational diabetes, an average of 2 hours 30 minutes' education occurred at the first combined visit with an average of a further 1.6 consultations bringing the average total to 2.8 hours. 18.7% of these patients were required to start insulin therapy, this requiring an additional 0.6 hours' education on average. The average duration of insulin therapy was 9.7 weeks with an average dose 47.7 IU/day. The authors estimated that around 150 monitoring sticks would be required. Unfortunately, the authors did not provide an estimate of the cost of this resource use.

Screening for gestational diabetes: cost-effectiveness studies full papers

Nicholson *et al.* (2005)¹²³ performed a cost-utility analysis of four alternative screening strategies:

- the 1-hour 50-g GCT
- the 100-g OGTT
- the 75-g OGTT
- no screening.

The GCT was taken to have a sensitivity of 80% and a specificity of 86%, with a positive result being a value equal to or greater than 7.8 mmol/l. The 75-g OGTT was assumed to have the same

sensitivity and specificity as the GCT of 80% and 86% respectively, with a positive result being a 2-hour value equal to or greater than 7.8 mmol/l. A positive result from the GCT required a confirmatory 100-g OGTT performed in the fasting state. The 100-g OGTT resulted in a positive result given: fasting 5.3 mmol/l, 1 hour 10.0 mmol/l, 2 hours 8.6 mmol/l; and 3 hours 8.1 mmol/l, and was taken to have a sensitivity and specificity of 100%.

Maternal outcomes included hypertensive disease, polyhydramnios and caesarean or vaginal delivery and their associated complications. Maternal complications modelled covered operative injury, endometritis, deep vein thrombosis, severe haemorrhage and hysterectomy. Neonatal outcomes included mild hypoglycaemia, macrosomia, respiratory distress syndrome, shoulder dystocia, no/mild morbidity, moderate morbidity and severe morbidity/death. Long term health states were defined within the modelling, these having the following quality of life values assumed (*Table 21*).

Cost estimation was within the US setting and adopted a social perspective, applying unit costs from Medicare and the Maryland Health Care Commission database. No real details of the model structure, probabilities of the various complications or the effectiveness of treatment for gestational diabetes upon the probabilities of the various complications were presented. The modellers adopted two models, one assessing the cost-effectiveness from the maternal perspective, the other from the neonatal perspective.

Based on an assumed prevalence of gestational diabetes of 4%, the least costly strategy was the 1-hour 50-g GCT followed by a confirmatory 100-g

OGTT. This applied within both the maternal model with an average cost of US\$2836 [£2181] and the neonatal model with an average cost of US\$77 [£59]. Given the differences in average costs between the maternal model and the neonatal model, this suggests that the costs of maternal complications were included in only the maternal model and the costs of the neonatal complications were included in only the neonatal model, though this cannot be stated with certainty.

The next cost strategy was the 100-g OGTT: within the maternal model an average cost of US\$2874 [£2210] and within the neonatal model an average cost of US\$98 [£75] resulted in a cost increase of US\$36 [£27.69] and US\$11 [£8.46], respectively. This was also more effective and yielded an estimated QALY gain of 0.001 QALYs on average in both models, to yield cost a cost-effectiveness estimate of US\$32,374 [£24,901] in the maternal model and US\$8252 [£6347] in the neonatal model. The 75-g OGTT was more costly than the 100-g OGTT, with cost increases of US\$59 [£45.38] and US\$13 [£10.00] for the maternal model and neonatal model respectively. But it was less effective than the 100-g OGTT so was dominated. A similar pattern applied to the no screening strategy, being US\$159 [£122] and US\$3 [£2.31] more expensive than the 100-g OGTT but also less effective. Details of methods and results are sparse, and no CIs are given for the very small QALY differences.

The ordering of effectiveness of the strategies naturally followed from the assumptions as to sensitivities and specificities. Given the assumed equal sensitivity and specificity for the 50-g GCT and the 75-g OGTT, and perfect sensitivity and specificity for the 100-g OGTT, the GCT followed by the 100-g OGTT would have the same number of false-negatives as the 75-g OGTT but no false-positives. The 100-g OGTT would have no false-negatives or false-positives.

Given this and the lack of clarity as to the model structure and input there is little confidence that can be placed in these results.

Larijani *et al.* (2003)¹²⁴ provided an estimate of the cost of alternative screening strategies among a sample of 2416 patients in four Iranian teaching hospitals, also calculating the cost per case detected within this sample. These patients were stratified into low, intermediate and high risk categories using the ADA criteria. The screening strategies compared were:

TABLE 21 Assumptions for utility values by Nicholson *et al.* (2005)¹²³

| | Utility |
|---------------------------------------|---------|
| Maternal health states | |
| Perfect health | 1.0 |
| Perfect health following hysterectomy | 0.9 |
| Death | 0.0 |
| Neonate health states | |
| No/mild morbidity | 1.0 |
| Moderate morbidity | 0.7 |
| Severe morbidity/death | 0.0 |

- universal screening
- selective screening, with low risk patients not being screened.

High risk patients were tested at their first prenatal visit and if not found to have gestational diabetes were tested again between gestation weeks 24 and 28. Intermediate and low risk patients were tested once between gestation weeks 24 and 28. The data were then used retrospectively to assess the effect of selective screening, with low risk women not tested. The 1-hour 50-g GCT was used for the screen with alternative thresholds of a 7.8-mmol/l cut-off and a 7.2-mmol/l cut-off, and was costed at US\$1.38 [£1.06]. Confirmation of positive results from the screen used the 100-g OGTT and a minimum of two of the standard cut-off criteria, and was costed at US\$4.19 [£3.22].

The overall prevalence of gestational diabetes in the sample was estimated as 4.7% with an assumption that universal screening with a 7.2-mmol/l cut-off was 100% sensitive, and the 100-g OGTT was 100% sensitive and specific. Universal screening with a 7.8-mmol/l cut-off was estimated to be 88% sensitive. Selective screening with 7.2-mmol/l cut-off was estimated to be 86% sensitive, while selective screening with a 7.8-mmol/l cut-off was estimated to be 77% sensitive. These led to: an average cost per patient across the entire sample, i.e. not restricted to those tested within the selective strategy; an average cost per case of gestational diabetes detected; and cost per additional case detected as shown in *Table 22*.

On the assumption that the cost per additional case conforms to the usual criteria for cost-effectiveness, the universal strategy with a cut-off of 7.8 mmol/l is extendedly dominated by the universal strategy with a cut-off of 7.2mmol/l. However, this dominance cannot be stated with confidence for any longer term measures of effectiveness and cost, given the restricted nature of the outcome measure and the costs included being restricted to the cost of testing.

Di Cianni *et al.* (2002)¹²⁵ undertook a retrospective study of two Italian patient samples:

- universal screening with those diagnosed with gestational diabetes being intensively treated ($n = 1338$)
- selective screening of high risk patients, with those diagnosed with gestational diabetes being conventionally treated ($n = 4035$).

As such, the paper reports a joint test of the impact of alternative screening and treatment strategies, rather than alternative screening strategies per se. Intensive treatment aimed to achieve tighter metabolic control of 5.0 mmol/l FPG and 6.7 mmol/l PPG as compared with 5.5 mmol/l FPG and 7.2 mmol/l PPG for conventional treatment.

It should also be noted that the samples were drawn from the same hospital, being primarily differentiated by time. Those universally screened related to the period 1994 to 1997 while those selectively screened related to the period 1987 to 1992. Furthermore, the screening tests applied also differed between the two groups: those universally screened received the 50-g GCT with a cut-off of 7.5mmol/l, with positive results being confirmed with the 3-hour 100-g OGTT; those selectively screened received only the 3-hour 100-g OGTT.

For the universal screening, 367 patients (27.4%) screened positive with 84 patients (22.9% of the screen-positives) being confirmed as having gestational diabetes to yield an overall diagnosis rate of 6.3%. A random sample of 250 of the 971 screening negative were tested with the 3-hour 100-g OGTT, this yielding an additional five patients diagnosed with gestational diabetes, implying a sensitivity of 81%. {Note that the authors report an implied sensitivity of 94% on the basis of $84/(84+5)$ rather than 81% as would be calculated by $84/[84+5 \times (971/250)]$. The authors also report a specificity of 78% but it is unclear how this has been calculated.} The additional five patients diagnosed were included in the analysis to yield a total of 89 patients for analysis.

TABLE 22 Cut-offs and screening costs: Larijani *et al.* (2003)¹²⁴

| Strategy | Cut-off | Cost per patient | Cost per case detected | Cost per additional case |
|---------------|------------|------------------|------------------------|--------------------------|
| (a) Universal | 7.2 mmol/l | US\$3.80 [£2.92] | US\$80.56 [£61.90] | US\$164 [£126] vs (c) |
| (b) Universal | 7.8 mmol/l | US\$3.21 [£2.47] | US\$77.44 [£59.51] | US\$595 [£458] vs (c) |
| (c) Selective | 7.2 mmol/l | US\$2.71 [£2.08] | US\$66.88 [£51.39] | US\$78 [£60] vs (d) |
| (d) Selective | 7.8 mmol/l | US\$2.39 [£1.84] | US\$65.63 [£50.43] | |

For selective screening the number of high risk patients was 600 out of the total patient sample of 4035. Ninety-three (15.5%) of these high risk patients tested positive to yield an overall prevalence of gestational diabetes of 2.3%. As a consequence, the selective testing of high risk patients appeared to miss significant numbers of patients with gestational diabetes in the non-high risk patient group.

Given the above, the characteristics of those diagnosed with gestational diabetes will have differed markedly between the two screening strategies. As a consequence, when reviewing the results of the paper, it should be borne in mind that the treatment strategies for those diagnosed with gestational diabetes also differed between the two strategies.

As would be expected, among those diagnosed with gestational diabetes through universal screening, followed by more intensive management, FPG showed a slightly better average level of 4.8 mmol/l as compared with 5.0 mmol/l among those diagnosed with gestational diabetes under selective screening, with this difference being reported as statistically significant, though clinically slight. Similarly, the percentages requiring insulin treatment, and the average insulin dose per day, were higher: 33% and 16.4 IU/day as compared with 7% and 13.6 IU/day, these differences again being reported as statistically significant. Neonatal and maternal morbidity was also typically better in those diagnosed through universal screening coupled with intensive management (Table 23).

The paper was not entirely clear in its reporting of costs, but it appears that the cost per diagnosed case under universal screening was €424 [£349] as compared with €406 [£334] for selective screening. However, there is a general lack of clarity around the costs within the paper, and these results

should not be taken at face value. Given the different treatment regimes of those diagnosed with gestational diabetes and there being no consideration within the paper of the outcomes of treatment among those not diagnosed with gestational diabetes, a proportion of whom will be false-negatives, there appears to be little that can be drawn from the results of Di Canni *et al.* (2002).¹²⁵

Poncet *et al.* (2002)¹²⁶ undertook a cost–consequence analysis of the four screening strategies:

- the 1-hour 50-g GCT among high risk women
- the 1-hour 50-g GCT among all women
- the 75-g OGTT among all women
- no screening

with a positive result from the GCT of a value equal to or greater than 7.2 mmol/l but requiring a confirmatory 100-g OGTT, this in turn being positive if two or more of the following applied: fasting 5.3 mmol/l, 1-hour 10.0 mmol/l, 2-hour 8.6 mmol/l; and 3-hour 7.8 mmol/l. These values appear to relate to the ADA cut-offs. The 75-g OGTT was positive if either the fasting level was equal to or greater than 5.5 mmol/l or the 2-hour level was equal to or greater than 8.0 mmol/l.

The high risk group was defined as having: a close family history of diabetes; age 35 years or over; a BMI of more than 27 kg/m²; previous pregnancy complicated by diabetes, pre-eclampsia or a fetal death after 3 months gestation; or previous delivery of a child of more than 4 kg.

The outcomes measured for the cost–consequence analysis were macrosomia, prematurity, perinatal mortality and hypertension disorders. Estimates of these were drawn from a pooled analysis of 38

TABLE 23 Outcomes from universal screening versus selective screening: Di Canni *et al.* (2002)¹²⁵

| | Universally screened (n=89) | Selectively screened (n=93) |
|------------------------------------|-----------------------------|-----------------------------|
| Gestation in weeks | 38.9 | 38.1 |
| Preterm delivery ^a | 27% | 29% |
| Caesarean sections ^a | 33% | 48% |
| Delivery with forceps ^a | 5% | 3% |
| Spontaneous delivery ^a | 61% | 49% |
| LGA ^a | 22% | 55% |
| a $p < 0.01$. | | |

papers from within the literature with the following probabilities being assumed (*Table 24*).

The figure for perinatal mortality for undiagnosed GDM seems high. The text of the article says this was based on a collection of 38 articles, published from 1973 to 1998, and that the perinatal mortality ranged from 0.6% to 16.4%. However the table gives a range of 6.4–26.4%, of which the baseline figure used, 16.4%, is mid-point. But then in *Table 4* of the Poncet *et al.* (2002)¹²⁶ article, perinatal mortality untreated is only 1.09%.

The presence of risk factors given the presence of gestational diabetes was estimated as 63.3% as compared with 51.6% for those without gestational diabetes. The success of dietary advice to cope with gestational diabetes was estimated as 73.6%. Agreement to the 50-g GCT was anticipated to be 66.3% as compared with 85.9% for the 75-g OGTT.

Resource use was drawn from a prospective study of 120 patients of the Rhône-Alpes region. Unit costs from the French social health insurance system were applied. These costs included the costs of sick leave starting from the 24th week of gestation to

discharge from maternity. Average costs per patient ranged from €5014 for an unscreened patient who did not have diabetes to €6026 for a patient screened as being diabetic with the 50-g GCT, having this confirmed with the 100-g OGTT and receiving insulin thereafter.

Within a decision tree analysis framework, the estimated costs and outcomes were as shown in *Table 25* and in turn resulted in the cost-effectiveness ratios for the screening strategies compared with no screening (shown in *Table 26*).

The strategies of testing all women rather than just high risk women naturally identified more women with diabetes, and, given the assumptions about acceptance rates of the tests, the 75-g OGTT performed better than the 50-g GCT. But costs naturally also increased with the higher rates of acceptance, and, as the paper did not estimate the downstream costs of the complications, the most accepted and so most effective test was also the most expensive.

Given the cost-consequence analysis adopted, and despite the authors claiming that the strategy

TABLE 24 Outcome frequencies: Poncet *et al.* (2002)¹²⁶

| | Macrosomia (%) | Prematurity (%) | Perinatal mortality (%) | Hypertension (%) |
|--------------------|----------------|-----------------|-------------------------|------------------|
| No diabetes | 9.8 | 9.0 | 0.62 | 8.2 |
| Treated diabetes | 16.8 | 10.3 | 0.93 | 16.3 |
| Untreated diabetes | 23.4 | 22.5 | 16.4 | 21.2 |

TABLE 25 Costs and outcomes: Poncet *et al.* (2002)¹²⁶

| | Cost | Macrosomia (%) | Prematurity (%) | Perinatal mortality (%) | Hypertension (%) |
|--------------------|---------------|----------------|-----------------|-------------------------|------------------|
| 50-g GCT high risk | €5030 [£3845] | 10.15 | 9.28 | 0.94 | 8.54 |
| 50-g OGTT all | €5039 [£3852] | 10.12 | 9.21 | 0.85 | 8.52 |
| 75-g OGTT all | €5135 [£3925] | 10.04 | 9.09 | 0.69 | 8.46 |
| No screening | €5018 [£3836] | 10.21 | 9.41 | 1.09 | 8.59 |

TABLE 26 ICERs: Poncet *et al.* (2002)¹²⁶

| | Macrosomia | Prematurity | Perinatal mortality | Hypertension |
|--------------------|-------------------|-------------------|---------------------|-------------------|
| 50-g GCT high risk | €21,069 [£16,105] | €9953 [£7608] | €7871 [£6017] | €28,674 [£21,919] |
| 50-g OGTT all | €23,135 [£17,685] | €10,965 [£8382] | €8663 [£6622] | €31,898 [£24,384] |
| 75-g OGTT all | €68,933 [£52,695] | €37,320 [£28,528] | €29,444 [£22,508] | €94,506 [£72,244] |

of screening high risk patients with the GCT has the best cost-effectiveness ratio, it cannot be concluded which strategy is the most cost-effective. There is also no obvious reason for the authors having excluded the strategy of screening high risk patients with the 75-g OGTT. The ranking of the strategies in terms of effectiveness was also critically dependent upon the assumed acceptance rates of 66.3% for the GCT as compared with 85.9% for the 75-g OGTT. No real detail was provided as to the source of these estimates, but it seems likely that the model would always predict a higher effectiveness but also a higher cost for the test with the higher acceptance rate.

Screening for gestational diabetes: cost-effectiveness studies abstracts

Lee *et al.* (2008)³⁷ briefly described a model comparing alternative cut-off values for a positive diagnosis of gestational diabetes when using the 75-g OGTT test, drawing on data from the HAPO trial¹⁹ for cut-offs of 6.1 mmol/l, 7.0 mmol/l and 7.8 mmol/l of 2-h PG. The potential prevention of pre-eclampsia and shoulder dystocia from a diagnosis of gestational diabetes was drawn from the ACHOIS trial.¹⁸ The model was long term, and possibly lifetime, estimating maternal and neonatal QALYs and costs from the societal perspective. Results indicated that lowering the threshold from the WHO recommended 7.8 mmol/l to 7.0 mmol/l had a cost-effectiveness of US\$76,000 [£38,108] which was deemed to be not cost-effective. Results were reported as being sensitive to prevalence rates, cost of management and the effect of treatment for gestational diabetes on pre-eclampsia.

Thung *et al.* (2007)¹²⁷ also undertook a modelling exercise comparing alternative cut-off values but for the 50-g GCT with the values of 7.2 mmol/l and 7.8 mmol/l being compared in a population with a prevalence of gestational diabetes of 3.3%, a third alternative of no screening also being considered. This found an average incremental cost of US\$8.09 [£4.24] using a cut-off of 7.2 mmol/l as compared with 7.8 mmol/l but also an average patient gain of 0.00054 QALYs to yield a cost-effectiveness estimate of US\$14,961 [£7845] per QALY. Perhaps surprisingly, the cost-effectiveness of the 7.8-mmol/l cut-off compared with no screening had a similar cost-effectiveness estimate of US\$12,269 [£6433]. The cost-effectiveness of the 7.2-mmol/l cut-off compared with the 7.8-mmol/l cut-off

rose above US\$50,000 [£26,218] per QALY if the prevalence of gestational diabetes fell below 0.8%. However they assumed a high baseline perinatal mortality of 20%, and in sensitivity analysis, cost-effectiveness was lost if this fell below 6%.

Summary of published studies

In brief:

- Costs are higher for pregnancies with gestational diabetes – about £1833 according to Chen *et al.* (2009).¹¹⁵
- Costs are lower for treatment with glibenclamide than with insulin, taking into account both drug costs and those of hypoglycaemia (Goetzl and Wilkins 2002¹¹⁷), by about \$166 [£142].
- Costs are higher in those who need to go on to insulin (Kitzmilller *et al.* 1998¹¹⁹).
- The economic analysis of the ACHOIS study (Moss *et al.* 2007¹²⁰) found that intervention with more intensive dietary advice, blood monitoring and insulin when required reported a cost per serious perinatal event avoided of £12,688. The (statistically not significant) impact upon perinatal mortality suggested a cost per life-year of £1376.
- Some studies (Lavin *et al.* 2001,¹²¹ Nicholson *et al.* 2005¹²³) found that screening with the GTC and then testing screen-positives with the OGTT was less costly than going straight to universal OGTT.

The NCC report for the NICE Guideline Development Groups

A high quality cost-effectiveness analysis was provided for the GDGs by the National Collaborating Centre for Women's and Children's Health. This analysis is included as Appendix D of the *Pregnancy in Diabetes* guideline.² Full details are available on the NICE website. In brief, it:

- developed a single model covering both screening and treatment
- had a wide range of 21 screening options, from none at all, to various combinations of risk factor selection (ADA criteria, BMI alone, ethnicity) and glucose testing, some using a screening test such as the GCT, others going direct to a 75-g OGTT

- incorporated false-positives and false-negatives
- included all costs of screening and treatment
- gave good detail of assumptions used
- used the outcomes data from ACHOIS for benefits of treatment.

The analysis found that two screening strategies dominated:

- selection by ADA criteria followed by the 75-g OGTT (ICER £3678)
- selection by high risk ethnicity followed by the 75-g OGTT (ICER £21,739).

A few issues arise with the modelling:

- There was not at the time, evidence on the use of metformin.
- The ACHOIS group had mild gestational diabetes, and their outcome rate untreated would be less than if the whole spectrum of GDM was used (as noted in the analysis).
- The perinatal mortality rate was increased in the control arm of ACHOIS, but there were only five deaths and the difference was not statistically significant. Perinatal mortality with an average loss of 25 QALYs (normal life expectancy discounted to present values) was the main factor in the ICERs. Sensitivity analyses with decreasing numbers of death rapidly raised the ICERs above what would normally be considered affordable – one fewer death raised the ICER for the first strategy above from £678 to £27,634.
- There was no screening strategy which used risk factors only – e.g. treating all women above 30 with lifestyle measures (perhaps justifiably since only a minority would have HGP).
- The 75-g OGTT was assumed to have 100% sensitivity and specificity.
- The analysis relied on single sources for accuracy of screening and diagnostic tests.
- The cost of severe hypoglycaemia (£500) may have been too high since it appeared to assume hospital attendance.
- The risk of hypoglycaemia with metformin was assumed to be the same as with glibenclamide.

- The analysis preceded HAPO, and was therefore based on the WHO criteria for GDM, and could not examine the bands of glucose level and outcomes.

It would therefore be useful to have an updated cost-effectiveness analysis for each of the HAPO categories, with screening strategies which incorporated selection by risk factors (not published for the seven HAPO categories yet) and by single tests such as FPG. The analysis would model the effect of treatment (HAPO women being untreated). The updated analysis could add the supra-HAPO glycaemic groups (e.g. FPG over 5.8 mmol/l).

Such an analysis would provide a better basis for recommendations. Our best guide at present is probably the abstract by Lee *et al.* (2008).³⁷

Conclusions

The evidence from cost-effectiveness studies shows that it is worth screening for and treating hyperglycaemia in pregnancy at and above the ACHOIS levels. The NICE modelling shows that two-stage screening, first with selection by risk factors and then with the 75-g OGTT is also cost-effective.

However, the economics studies don't yet help with our most difficult issue – at what level of BG does intervention become cost-effective. The study by Lee *et al.* (2008)³⁷ addresses that issue, but is only available as an abstract. We recommend that the team which did the modelling for the NICE guidelines group should be asked to update their analysis.

Inevitably, modelling requires assumptions, about probabilities and utilities, and any estimate will have confidence intervals. So even the best modelling may not be able to come up with a neat solution to the continuum problem.

Chapter 5

Discussion

Changes since the previous Health Technology Assessment review in 2002

The evidence base has improved since the last HTA review in 2002,³ and since the main review for the NICE guidelines was done in 2007.² One of the main changes is the evidence on the continuum of risk, principally from the HAPO study¹⁹ but also supported by a number of smaller studies which examined outcomes for women on the borderlines of GDM as previously defined.

A second change is the evidence on the benefits of treatment at lower levels, from the ACHOIS study,¹⁸ and from the trial by Landon *et al.* (2008/9).^{20,50}

A third change is on mode of treatment, with good evidence that women who fail to control HGP on lifestyle measures alone can be safely and effectively treated with oral agents such as metformin or glibenclamide rather than going directly to insulin, though some women will still need insulin. There is also more evidence on the benefits of lifestyle change – calorie control, low glycaemic index foods, and physical activity.

The demonstration of the continuum by the HAPO study¹⁹ was predicted in the last HTA review,³ but we now have really strong evidence for it. That unfortunately causes problems in deciding on the level of BG at which we should intervene. There is no easy clinical threshold for intervention. It could be argued that since the first line of treatment would be diet and physical activity, it would not matter if we adopt a low threshold and perhaps give lifestyle advice to some women unnecessarily, but there is some evidence that the diagnosis itself can generate anxiety.

One way forward is through cost-effectiveness analysis, to determine the level, probably in terms of HAPO category, at which intervention is cost-effective. This is recommended below, under research needs.

Other perhaps interim options include intervention based on relative risk, i.e. intervening at the

glucose level (or HAPO category) at which the risk is increased by a certain amount – say by 50%. This is rather arbitrary and might mean treating most women. For birthweight over the 90th percentile, the OR was 1.72 in HAPO category 3. It would be better to treat based on absolute risk.

Revisiting the National Screening Committee criteria

Some of the criteria which were not met in the last HTA review,³ are now met.

The condition should be an important health problem. Met. The condition has become more important because of rising prevalence and the HAPO demonstration of adverse outcomes over a much wider range of BG.

All cost-effective primary prevention interventions should have been implemented as far as possible. Debatable. Public health campaigns have not prevented the rise in general population obesity, but primary prevention has not been tried specifically in women planning pregnancy who may be more motivated for the sake of their babies.

The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed. Not yet met, pending further cost-effectiveness analysis post-HAPO.

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals. Partially met, but further analysis required. HAPO has shown that a single measure of BG is highly predictive, and it is possible that FPG alone could be used.

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment. Met. There are effective treatments, including diet, physical activity, glibenclamide and metformin, and

insulins. It is also reasonable to assume that missing the therapeutic window in early third trimester may lead to poorer outcomes. Some fetuses are macrosomic by the time of screening.

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment offered. Met. The ACHOIS trial¹⁸ has shown that intervention at lower levels is cost-effective. Trials of oral drugs have shown they are safe and effective, as well as being cheaper and preferred by patients. But there is still some doubt over the threshold for intervention.

There must be evidence from high-quality RCTs that the screening programme is effective in reducing mortality or morbidity. Not met – still no RCTs of screening versus no screening.

The benefit from the screening programme should outweigh the physical and psychological harm caused by the test, diagnostic procedures and treatment. Partly met. The balance has swung towards easier testing and easier treatment, which coupled with increasing prevalence should shift the balance towards benefit.

The opportunity cost of the programme should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money). Met for some groups following the economic analyses by the ACHOIS group and for the NICE GDGs, but still some uncertainties to be resolved.

Prevention of gestational diabetes mellitus

Could we tackle the problem at source, by reducing overweight and obesity in pregnancy? There might be two approaches. The first would be by health education campaigns aimed at persuading women to control weight before conception, and not to put on too much weight during pregnancy. The second could be opportunistic advice given to women attending for contraceptive services.

A recent systematic review found that for every one point increase in BMI, the prevalence of GDM increased by 0.9%.¹²⁸ The ORs for overweight and obese women were 1.97 and 3.01, respectively.

Recent reviews and guidelines

The German IQWiG published its review of screening for gestational diabetes in August 2009.⁴⁶ The summary in English noted that there was clear evidence of benefit of treating GDM. It noted that there was a lack of suitable screening studies, but it concluded that ‘an indication can be indirectly deduced that screening for gestational diabetes leads to a reduction in perinatal complications.’

The SIGN guideline¹ notes the lack of international consensus over screening for GDM. It concludes that given present evidence, the best approach at present was two-stage screening, firstly by risk factors, and secondly by 75-g OGTT at 24–28 weeks in women selected by risk factors. The SIGN guideline considered the threshold for intervention, and noted the lack of an international consensus. It recommended that the threshold for intervention should be at a level where the RCTs showed an impact not just on birthweight, but on outcomes including shoulder dystocia and caesarean section.

The International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel advocated testing of all women with a 75-g OGTT at 24–28 weeks, unless they had been found to have abnormal glucose levels earlier in pregnancy.¹²⁹ The IADPSG did not take cost-effectiveness into account, but it noted that further analysis of the HAPO data might allow identification of low risk pregnancies where screening might not be required.

The International Diabetes Federation issued a ‘global guideline’ in 2009 which favoured universal testing of all women but issued a compromise recommendation of testing for GDM for all women at 26–28 weeks, ‘unless a selective process based on risk factors is deemed more appropriate’.¹³⁰

Research needs

It appears from the HAPO study¹⁹ that screening could use FPG. However we need further analysis before we can adopt that policy.

Research need 1: analysis of HAPO data to determine how many women in categories 1–4 by FPG are in categories 5 to 7 by post-load PG.

HAPO data could also be used to address the question of selective or universal screening, by comparing risk factors, and different thresholds, with each category. The hypothesis might be that women with risk factors are more likely to be in the higher categories.

There is one issue which needs to be considered if we relied on FPG for screening, which is that of later maternal T2DM. Retnakaran *et al.* (2009)¹³¹ found that FPG was better for predicting LGA infants, but that the post-load PGs were better for predicting post-gestational T2DM. The risk of T2DM has been thoroughly reviewed by Bellamy *et al.* (2009),¹³² with a meta-analysis showing that women who had had GDM (defined in various ways) had a relative risk of 7.4 compared with those who were normoglycaemic during pregnancy.

Research need 2: can risk factors identify a group of women whose risk of adverse outcomes is very low and who need not be screened?

The third research need concerns screening at booking clinic and how that should be done. At this stage we would be looking for pre-gestational diabetes or non-diabetic hyperglycaemia, so HbA_{1c} might be useful. It has been recommended by the National GDM Technical Working Party in New Zealand.¹³³

Research need 3: is HbA_{1c} a useful test at booking clinic for detecting pre-gestational diabetes, and also pre-gestational insulin resistance likely to be followed by HGP?

The above needs concern how best to screen, but an unresolved issue is the level of glucose at which intervention is worthwhile, which requires a cost-effectiveness analysis. This has been addressed by Lee *et al.* (2008)³⁷ (whose results are available only as an abstract). It needs to be repeated in a UK context, by re-running the National Collaborating Centre for Women's and Children's Health modelling with updated assumptions and for the seven HAPO categories.

Research need 4: at which HAPO category does treatment become cost-effective, taking into account infant and maternal outcomes, and treatment with the cheaper oral agents when lifestyle measures fail, with insulin being used only when the oral drugs fail?

As mentioned above, it would be better to reduce the problem at source, by persuading women to

achieve normal weight before conception. Trials of targeted health education are necessary.

Research need 5: could a health education campaign raise awareness of the problems of HGP amongst women of child-bearing age, and reduce the number becoming pregnant while overweight? Or at least reduce the BMI, and hence the risk?

The time continuum: research need 6: given the increasing age and weight of mothers-to-be, should screening start earlier? Screening is usually done at 24–28 weeks. Agarwal *et al.* (2007)¹³⁴ described GDM as a form of T2DM which comes on over months not years. Are there studies which report the prevalence of HGP by gestational age, perhaps at 2-week intervals? Could such studies identify optimum time to screen, perhaps depending on age and BMI? Several commentators have noted that there can be delays between screening, diagnostic testing and treatment, and that these can occur during the 'therapeutic window' and hence result in poorer outcomes.

Research need 7: the HAPO study¹⁹ recorded head circumference. Given that the reported macrosomic babies will consist of a mixture of large healthy babies and truly macrosomic ones, the HAPO investigators could isolate the abnormal macrosomic ones by comparing weight with head circumference. This might allow a more refined analysis of macrosomia by HAPO category.

Research need 8: Reece *et al.* (2009)¹³⁵ report that in the USA, the prevalence of pre-gestational diabetes in pregnancy has increased, but that of GDM has not. Conversely, Massicotte *et al.* (2009)¹³⁶ reported that the prevalence of GDM in Canada had tripled over the last 10 years. It would be of interest to monitor trends in the UK.

One issue, raised by one of the peer reviewers for this report, was whether GDM should be defined on the basis of glucose at all. It may seem odd to define any diabetic condition on the basis of anything other than glucose, but the referee's point was presumably that we are looking at a metabolic condition with abnormalities in physiological variables other than glucose, and that some of these other variables, such as lipids, might have a stronger relationship with adverse outcomes than glucose. Hadden and McLaughlin in a 2009 review note that normal pregnancy is hyperlipidaemic, and that birthweight is positively correlated with both plasma triglycerides and free fatty acid concentrations.¹³⁷ Is what we call GDM, part of a

set of 'metabolic syndromes of pregnancy', with some women displaying changes more in glucose homeostasis, but others more in lipids, and some in both?

Ongoing research

- Two Cochrane protocols have been published and reviews are presumably under way:
 - Alternative strategies for diagnosing gestational diabetes mellitus to improve maternal and infant health.¹³⁸
 - Screening for gestational diabetes to improve maternal and child health.¹³⁹

The first is considering different screening tests. The protocol of the second suggests that it is doing the same, but the protocol for the first says that the second one is about whether screening should be selective or universal.

- A Finnish cluster-randomised controlled trial (ISRCTN33885819), described as due to complete at the end of 2008, used a lifestyle intervention (intensive dietary advice, counselling on physical activity, frequent contacts, and a group session) to reduce the prevalence of GDM and of large babies in women at risk.
- A Stanford University study is comparing the 50-gm glucose tolerance test, followed by a blood test 1 hour later, with 7-day continuous glucose monitoring (NCT00850135). The aim is to determine which test correlates better with adverse pregnancy outcomes as well as which one more accurately identifies patients at risk for adverse pregnancy outcomes.
- A University of North Carolina trial (NCT00835861), described as a pilot, is randomising women, with either pre-gestational T2DM or GDM diagnosed before 20 weeks, to metformin or insulin. The hypothesis is that metformin will provide glycaemic control that is equivalent to insulin in these women.
- A Swedish study (NCT00625781) is randomising pregnant women with IGT (FPG < 7 mmol/l and 2-hour PG between 10.0 and 12.2 mmol/l) to either insulin or diet. The purpose is to evaluate whether treatment of women close to normoglycaemia reduces children's birthweight and neonatal morbidity.
- A study in Texas (NCT00744965) is randomising women with 'mild gestational diabetes' (PG after 50-g GCT \geq 140 mg/dl but

FPG of \leq 105 mg/dl) to glibenclamide or diet alone. The hypothesis being tested is that in women with mild GDM, use of glibenclamide in addition to diet and nutritional counselling lowers mean infant birthweight by 200 g as compared with diet and nutritional counselling alone.

- In São Paulo, a recently completed trial (NCT00815828) has tested the effect of a programme of resistance exercises in women with gestational diabetes. Primary outcome measures is the comparison of the frequency of women who use insulin in the group who participate in the exercise programme with the group that don't do the exercises.
- A Swedish trial currently under way is comparing a low glycaemic index carbohydrate diet versus no dietary intervention in pregnant women whose first baby was macrosomic. The aim is to prevent recurrence of a large baby (ISRCTN54392969).
- A randomised controlled trial in Tennessee comparing a combined metformin and glibenclamide tablet versus insulin in pregnant women with gestational or T2DM was described as due for completion at the end of 2008 (NCT00371306). The hypothesis is that patients will have similar or improved BG control on the combined oral agents as compared with control on insulin.
- An NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) trial to investigate the effects of a motivationally tailored, individually targeted 12-week physical activity intervention on the risk of GDM in women at high risk of the condition currently recruiting women (NCT00728377). The hypothesis being tested is that an exercise intervention is an effective tool for preventing GDM among women with a history of GDM.
- A Danish study is recruiting pregnant women with BMI over 30, who will be randomised to lifestyle intervention or a control group. The lifestyle intervention will include both diet (individual dietary counselling) and exercise (weekly aerobic classes) (NCT00530439). The primary outcome measures will be caesarean section, GDM, hypertension/pre-eclampsia, LGA and admission to NICU.

Conclusions

Treatment

There is more good evidence (not detailed in this review) that lifestyle measures can be effective, and those should still be first line.

We now have good evidence that glibenclamide and metformin are safe and effective (as well as being preferred by women) and cheaper, so they should now be second line, with insulin third line.

We recommend that NICE update their guidelines with the new evidence.

Screening

It looks increasingly as if FPG could be the test of choice, thereby avoiding cumbersome testing of glucose tolerance. However some further analysis of HAPO data is required to check on how many women in HAPO categories 1–4, were in higher categories by post-load levels.

A fasting level of 5.0 mmol/l would identify about 10% of all pregnancies as having hyperglycaemia.

Because some uncertainties remain which could be resolved by further analysis of existing data, and because that might not take very long, we recommend that NSC wait for the results before reviewing their policy on screening for HGP.

Prevention

There is a need to tackle the problem at source by encouraging healthier lifestyles in women in the childbearing years.



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About the Aberdeen HTA group

The Aberdeen Health Technology Assessment Group is part of the Institute of Applied Health Sciences (IAHS), which is part of the College of Medicine and Life Sciences of the University of Aberdeen. The Institute of Applied Health Sciences is made up of discrete but methodologically related research groups. The HTA Group is drawn mainly from the Health Services Research Unit, Public Health, and the Health Economics Research Unit. In the last RAE (Research Assessment Exercise), Aberdeen was first equal with the University of York in the health services research unit of assessment.

The HTA Group carries out independent health technology assessments [Technology Assessment Reports (TARs)] for the NIHR HTA programme, which commissions TARs for NICE and other bodies, such as the NSC. It also carries out

evidence reviews to support the NICE Single Technology Appraisal programme.

Particular interests include evaluation of non-pharmacological technologies, screening and diabetes. Previous TARs from Aberdeen include:

- Inhaled insulin for diabetes (for NICE)¹⁴⁰
- Continuous subcutaneous insulin infusion (NICE)¹⁴¹
- Screening for type 2 diabetes (NSC and Department of Health)¹⁴²
- Newer drugs for type 2 diabetes (NICE)¹⁴³
- Self-monitoring of blood glucose in type 2 diabetes (Department of Health).¹⁴⁴

We also do Cochrane reviews on diabetic topics.

Contribution of authors

Norman Waugh drafted Chapters 1, 3 and 5. Christine Clar, Pamela Royle and Rob Henderson drafted Chapter 2. Ewen Cummins drafted Chapter 4. Pamela Royle carried out literature searches. Donald Pearson, Robert Lindsay and David Hadden provided expert clinical advice and commented on drafts. Pamela Royle and Norman Waugh edited the final document.



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Appendix I

Search strategy and flow of studies

Searches for treatment of hyperglycaemia in pregnancy

Papers published in full

The database searches below were undertaken as a part of a wider search on all aspects of hyperglycaemia in pregnancy:

Ovid MEDLINE: 1996 to November Week 3, 2008 and MEDLINE In-Process & Other Non-Indexed Citations 12 January, 2009

1. exp Diabetes, Gestational/
2. (gestation* adj2 diabet*).tw.
3. exp Hyperglycemia/
4. exp Pregnancy/
5. 4 and 3
6. ((hyperglycemia or hyperglycaemia) adj4 pregnan\$.tw.
7. 6 or 1 or 2 or 5
8. ((glucose tolerance or impaired fasting glucose) adj3 pregnan*).tw.
9. (diabet\$adj2 pregnan\$.m_titl.
10. 8 or 7 or 9
11. limit 10 to (english language and yr="2000 - 2009")

Number retrieved = 1120

Ovid EMBASE: 1996 to 2008 Week 52

1. (gestation* adj2 diabet*).tw.
2. exp Hyperglycemia/
3. exp Pregnancy/
4. 3 and 2
5. ((hyperglycemia or hyperglycaemia) adj4 pregnan\$.tw.
6. exp Pregnancy Diabetes Mellitus/
7. 6 or 4 or 1 or 5
8. (diabet* and pregnan*).m_titl.
9. ((glucose tolerance or impaired fasting glucose) adj3 pregnan*).tw.
10. 8 or 7 or 9
11. limit 10 to (english language and yr="2000 - 2009")

Number retrieved = 1749

Cochrane Library 2008 issue 4

“gestational diabetes in Title, Abstract or Keywords or (hyperglycaemia or hyperglycemia) and pregnan* in Title, Abstract or Keywords”

Number retrieved: Cochrane reviews = 11; other reviews = 5; clinical trials = 267; technology assessments = 5; economic evaluations = 21

Web sites

- NICE: www.nice.org.uk/
- NHS Quality Improvement Scotland: www.nhshealthquality.org/

The bibliographic details of all records retrieved from above searches were downloaded into the bibliographic software database REFERENCE MANAGER version 11. Duplicates and records not relevant to the topic were removed. This resulted in 757 records.

A search within the REFERENCE MANAGER database was done using the strategy:

“Treatment or management or drug therapy or insulin or glibenclamide or glyburide or pharmacolog* or (oral and agent*) or (oral and drug*)”

This retrieved 77 records.

Searches for meeting abstracts

Web of Science: April 2009

Search strategy

Title=(gestational diabetes or (hyperglyc* and pregnan*)) and (metformin or insulin or glyburide or glibenclamide or oral or drug or pharmacolog*)

Refined by: Document Type=(MEETING ABSTRACT)

Timespan=2000-2009. Databases=SCI-EXPANDED.

Number retrieved = 127

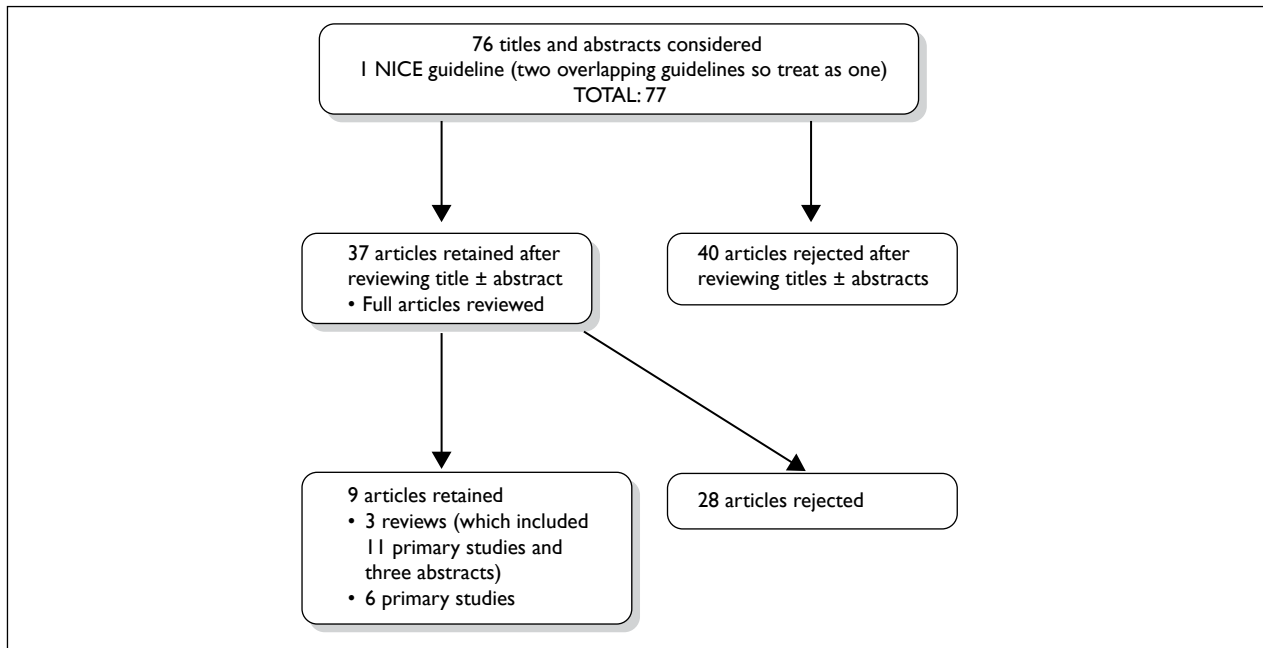
Of these, 45 were selected.

**Diabetes UK meeting abstracts
2002–2009**

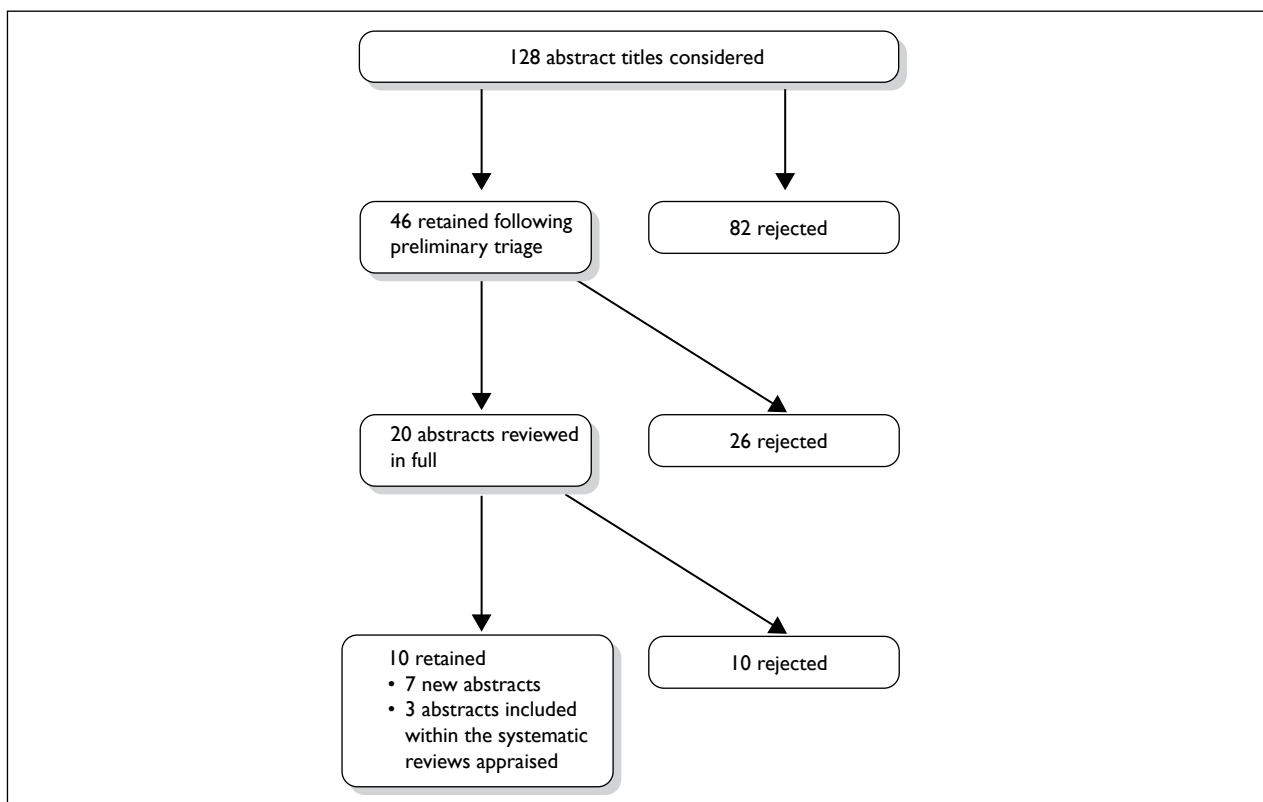
These were manually searched and one additional abstract was found.

Therefore, 128 abstracts were initially identified, and 46 were considered following preliminary triage.

**Search results
Papers published in full**



Meeting abstracts



Searches for cost-effectiveness studies

MEDLINE

Ovid MEDLINE 1996 to June Week 3, 2009 and MEDLINE In-Process & Other Non-Indexed Citations 30 June, 2009

1. "Costs and Cost Analysis"/
2. "cost of illness"/
3. exp Economics/
4. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$).tw.
5. exp quality-adjusted life years/
6. (qaly\$or EQ5D or EQ-5D or euroqol or euro-qol).tw.
7. 6 or 4 or 1 or 3 or 2 or 5
8. exp Diabetes, Gestational/
9. (gestation* adj2 diabet*).tw.
10. exp Hyperglycemia/
11. exp Pregnancy/
12. 11 and 10
13. ((hyperglycemia or hyperglycaemia) adj4 pregnan\$).tw.
14. 13 or 8 or 9 or 12
15. ((glucose tolerance or impaired fasting glucose) adj3 pregnan*).tw.
16. (diabet\$adj2 pregnan\$).m_titl.
17. 15 or 14 or 16
18. 7 and 17
19. limit 18 to english language

151 retrieved

EMBASE

Ovid EMBASE 1996 to 2009 Week 26

1. exp health economics/
2. (pharmacoeconomic\$or pharmaco-economic\$or cost\$or economic\$).tw.
3. (qaly\$or EQ5D or EQ-5D or euroqol or euro-qol).tw.
4. exp Quality-Adjusted Life Years/
5. 4 or 1 or 3 or 2
6. (gestation* adj2 diabet*).tw.
7. exp Hyperglycemia/
8. exp Pregnancy/
9. 8 and 7
10. ((hyperglycemia or hyperglycaemia) adj4 pregnan\$).tw.
11. exp Pregnancy Diabetes Mellitus/
12. 11 or 9 or 6 or 10
13. (diabet* and pregnan*).m_titl.
14. ((glucose tolerance or impaired fasting glucose) adj3 pregnan*).tw.
15. 13 or 12 or 14
16. 15 and 5
17. limit 16 to english language

300 retrieved

CRD databases (including NHS EED) July 2009

Searched using 'gestational diabetes' – no additional studies retrieved.

Web of Science with Conference Proceedings 01/07/2009

| | | |
|----|-----------|--|
| #5 | 74 | #4 AND #3 Databases=SCI-EXPANDED Timespan=2000-2009 |
| #4 | 2923 | #2 OR #1 Databases=SCI-EXPANDED Timespan=2000-2009 |
| #3 | > 100,000 | Topic=(cost* or economic* or pharmaco-economic* or pharmacoeconomic*) Databases=SCI-EXPANDED Timespan=2000-2009 |
| #2 | 244 | Topic=((hyperglycaemia or hyperglycemia) same pregnan*) Databases=SCI-EXPANDED Timespan=All Years |
| #1 | 4551 | Topic=(gestational same diabetes) Databases=SCI-EXPANDED Timespan=All Years |

Appendix 2

Characteristics of systematic reviews

| Review | Inclusion criteria and methodology | Included studies | Quality |
|--|--|---|---|
| <p>Moretti 2008⁵⁴</p> <p>Canada</p> <p>Focus: safety of glibenclamide use in pregnancy in the treatment of gestational diabetes compared with insulin therapy</p> <p>Funding: Canadian Institutes of Health Research</p> | <p>INCLUSION CRITERIA</p> <p>Study design: not specified [comparative observational or randomised controlled trial (RCT)]</p> <p>Participants: patients with gestational diabetes</p> <p>Interventions: glibenclamide-exposed group and insulin-exposed group</p> <p>Outcomes: perinatal outcomes</p> <p>METHODOLOGY</p> <p>Search strategy: MEDLINE, EMBASE, Biosis; 1950 to October 2006; reference lists of articles retrieved; search terms indicated</p> <p>Study selection: method not reported; trial flow reported</p> <p>Quality assessment: not reported</p> <p>Data extraction: method not reported; items extracted reported</p> <p>Meta-analysis: yes</p> <p>Data analysis: odds ratios (ORs) or weighted mean differences (WMDs) and 95% confidence intervals (CIs); random effects model; heterogeneity assessment; limited summary in tables</p> <p>Subgroups/sensitivity analyses: none</p> | <p>Number of included trials: nine</p> <p>Number of participants: 745 glibenclamide-exposed and 637 insulin-exposed</p> <p>TRIALS</p> <p>Design: one RCT, four prospective cohort, four retrospective cohort</p> <p>Duration: not reported</p> <p>Quality: not reported</p> <p>Origin: not reported</p> <p>Funding: not reported</p> <p>PARTICIPANTS</p> <p>No information on participants provided; range of participants per study group 7–268</p> <p>INTERVENTIONS</p> <p>Treatment typically started at 24 weeks of gestation, typical daily dose of glibenclamide 5–10 mg (insulin treatment not described)</p> <p>OUTCOMES</p> <p>Macrosomia (birthweight >4000g), birthweight, large for gestational age (LGA) (>90th percentile for gestational age), gestational age at birth, neonatal hypoglycaemia, rate of ICU admission</p> | <p>Inclusion criteria described: yes</p> <p>Details of literature search given: yes</p> <p>Study selection described: no</p> <p>Data extraction described: partly</p> <p>Study quality assessment described: no</p> <p>Study flow shown: yes, narratively</p> <p>Study characteristics of individual studies described: no</p> <p>Quality of individual studies given: no</p> <p>Results of individual studies shown: yes</p> <p>Statistical analysis appropriate: yes</p> <p>OVERALL QUALITY: low</p> |

| Review | Inclusion criteria and methodology | Included studies | Quality |
|---|--|--|---|
| <p>NICE guideline 2008² UK Focus: guideline on diabetes in pregnancy; includes section on gestational diabetes and its treatment (including treatment with oral agents) Funding: UK National Institute for Health and Clinical Excellence (NICE)</p> | <p>INCLUSION CRITERIA Study design: evidence according to hierarchy systematic reviews, RCTs, observational studies Participants: patients with gestational diabetes (for relevant part of review) Interventions: oral anti-diabetic treatment Outcomes: range of maternal and neonatal outcomes listed</p> <p>METHODOLOGY Search strategy: searches from database inception to March 2007: MEDLINE, EMBASE, CINAHL, and PsycINFO; Cochrane Library (1, 2007); only English-language articles assessed Quality assessment: NICE guidelines manual (presumably) Data extraction: NICE guidelines manual (presumably), no details reported Meta-analysis: no Data analysis: text, evidence tables Subgroups/sensitivity analyses: none</p> | <p>Number of included trials: six relevant (three RCTs, three observational) Number of participants: 1108</p> <p>TRIALS Design: three RCTs, three cohort Duration: not reported Quality: not reported Origin: USA, Brazil (where reported) Funding: not reported</p> <p>PARTICIPANTS No details on participants provided; range of participants per study group 19–268</p> <p>INTERVENTIONS No details of treatments; one RCT glibenclamide vs insulin, one RCT glibenclamide vs acarbose vs insulin, one RCT metformin vs insulin, three cohort studies glibenclamide vs insulin</p> <p>OUTCOMES <i>Maternal:</i> blood glucose (BG), hypoglycaemia, pre-eclampsia; <i>neonatal:</i> macrosomia, birthweight, LGA, gestational age at birth, neonatal hypoglycaemia, rate of ICU admission, lung complications, fetal anomalies, birth injuries, BG</p> | <p>Inclusion criteria described: yes Details of literature search given: yes Study selection described: no Data extraction described: yes Study quality assessment described: no Study flow shown: no Study characteristics of individual studies described: partly Quality of individual studies given: partly Results of individual studies shown: partly Statistical analysis appropriate: N/A OVERALL QUALITY: low/moderate</p> |

| Review | Inclusion criteria and methodology | Included studies | Quality |
|---|--|---|--|
| <p>Nicholson 2009⁵⁵ USA</p> <p>Focus: comparative risks and benefits of oral agents versus insulin in women with gestational diabetes mellitus</p> <p>Funding: Agency for Healthcare Research and Quality</p> | <p>INCLUSION CRITERIA</p> <p>Study design: RCT or observational study</p> <p>Participants: women with gestational diabetes mellitus; oral glucose tolerance test (OGTT) used to confirm diagnosis of gestational diabetes</p> <p>Interventions: oral diabetes agent vs insulin</p> <p>Outcomes: <i>maternal outcomes</i>: caesarean delivery, glycaemic control, haemorrhage, hypoglycaemia, operative vaginal delivery, perineal tears, pre-eclampsia, weight; <i>neonatal outcomes</i>: anoxia, birth trauma, birthweight, congenital malformation, hyperbilirubinaemia, hypoglycaemia, LGA, macrosomia, mortality, neonatal intensive care unit admissions (NICU), respiratory distress syndrome, small for gestational age (SGA), shoulder dystocia</p> <p>METHODOLOGY</p> <p>Search strategy: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cumulative Index of Nursing and Allied Health Literature; inception to January 2007, update to May 2008; reference lists of included studies and relevant reviews; hand-searching of 13 relevant journals; search strategies given in full AHRQ review; non-English articles excluded</p> <p>Study selection: done by two independent reviewers; study flow shown</p> <p>Quality assessment: Jadad criteria for RCTs, STROBE criteria for observational; GRADE for rating the evidence; used by two reviewers independently</p> <p>Data extraction: done by two independent reviewers using standardised forms</p> <p>Meta-analysis: yes, for infant weight only (not enough comparable data for other outcomes)</p> <p>Data analysis: random effects model (DerSimonian and Laird⁴⁵); heterogeneity testing; summary tables</p> <p>Subgroups/sensitivity analyses: sensitivity analysis for dominance of any one study</p> | <p>Number of included trials: nine</p> <p>Number of participants: RCTs: 1229, <i>observational</i>: 831</p> <p>TRIALS</p> <p>Design: four RCTs, five cohort studies</p> <p>Duration: not reported</p> <p>Quality: RCTs: two described randomisation scheme, none were blinded, two reported participants withdrawals and reasons for losses to follow-up, two reported intention to treat (ITT) analysis; <i>cohort studies</i>: all had reproducible eligibility criteria and consecutive sample of participants, none reported power analyses, only one study described losses to follow-up and only one study described handling of missing data</p> <p>Origin: RCTs: India, Brazil, USA, Australia/New Zealand; <i>cohort studies</i>: USA</p> <p>Funding: not reported</p> <p>PARTICIPANTS</p> <p>Age: RCTs: 24.9–33.5 years</p> <p>Body mass index (BMI): RCTs: (pre-pregnancy) 22.82 to 27.3 kg/m² (where reported)</p> <p>Hyperglycaemia: no details</p> <p>HbA_{1c}: not reported</p> <p>Gestational age: RCTs: 22.5–25 weeks (where reported)</p> <p>INTERVENTIONS</p> <p>RCTs: two RCTs: insulin vs glibenclamide, one RCT: insulin vs glibenclamide vs acarbose, one RCT: insulin vs metformin; all cohort studies were concerned with glibenclamide vs insulin</p> <p>OUTCOMES</p> <p>RCTs: <i>maternal outcomes</i>: maternal hypoglycaemia, maternal glycaemic control, caesarean section; <i>neonatal outcomes</i>: hypoglycaemia, hyperbilirubinaemia, macrosomia, LGA, SGA, prenatal mortality, birthweight, other (including congenital malformation, NICU admission, birth trauma)</p> | <p>Inclusion criteria described: yes</p> <p>Details of literature search given: yes</p> <p>Study selection described: yes</p> <p>Data extraction described: yes</p> <p>Study quality assessment described: yes</p> <p>Study flow shown: yes</p> <p>Study characteristics of individual studies described: yes</p> <p>Quality of individual studies given: yes</p> <p>Results of individual studies shown: yes</p> <p>Statistical analysis appropriate: yes</p> <p>OVERALL QUALITY: high</p> |

Values are mean \pm SD unless indicated otherwise.

Appendix 3

Results of systematic reviews

The NICE guideline 2008² did not report summaries for individual outcomes but only descriptions of individual studies already included in the table below.

| Review | Outcome | N studies | Result of meta-analysis/review | p-value | Comments |
|---------------------------------|----------------------------|----------------------------|---|---|--|
| Maternal outcomes | | | | | |
| <i>Insulin vs glibenclamide</i> | | | | | |
| Nicholson 2009 ⁵⁵ | Maternal hypoglycaemia | Three RCTs | No hypoglycaemia requiring hospitalisation in one study; finger stick glucose less than 2.2 mmol/l (40 mg/dl) in 20% in insulin group vs 2% in glibenclamide group in Langer 2000 ⁶⁸ | Significantly more hypoglycaemia in insulin group in one of three RCTs | |
| | | Two cohort | Jacobsen 2005: ⁷⁵ FBG less than 3.3 mmol/l (60 mg/dl) 0.08% with insulin vs 0.2% with glibenclamide; Yogev 2004: ⁷⁸ finger stick glucose less than 2.8 mmol/l (50 mg/dl), with or without symptoms 0% with diet vs 63% with insulin vs 28% with glibenclamide | Both significant, but one more hypoglycaemic with glibenclamide and one more with insulin | |
| | Maternal glycaemic control | Three RCTs Three cohort | Various measures reported | NS | NS |
| | | Two RCTs | Caesarean section range 23–52% | NS | In Jacobson 2005 ⁷⁵ glucose values at baseline where also higher in the insulin group; Chmait 2004 ⁷⁹ compared groups of glibenclamide failure with glibenclamide success |
| | | Three cohort | Caesarean section range 34–43% | NS | Jacobson 2005 ⁷⁵ and Chmait 2004 ⁷⁹ significantly higher values for insulin than glibenclamide for most glycaemic measures [fasting blood glucose (FBG), post-prandial (PPG)]; Yogev 2004 ⁷⁸ NS |
| | Pre-eclampsia | One RCT | Pre-eclampsia range 5.5–7.0% | NS | |
| | | One cohort | 6% in insulin group vs 12% in glibenclamide group; OR 2.32 (95% CI 1.17 to 4.63) | p < 0.05 | |
| <i>Insulin vs metformin</i> | | | | | |
| Nicholson 2009 ⁵⁵ | Maternal glycaemic control | One RCT | FBG 5.1–5.2 mmol/l (91.8–93.6 mg/dl); 2-hour PPG 6.2 mmol/l (111.6 mg/dl) with metformin, 6.4 mmol/l (115.2 mg/dl) with insulin | Significantly lower 2-hour PPG with metformin than insulin, p = 0.03; NS for FBG | |
| | Caesarean section | One RCT | Caesarean section range 36–38% | NS | |
| | Preeclampsia | One RCT | 5.5–7.0% | NS | |

| Review | Outcome | N studies | Result of meta-analysis/review | p-value | Comments |
|---|--|-----------|--------------------------------------|---------|---------------------------------|
| <i>Insulin vs acarbose</i> | | | | | |
| Nicholson 2009 ⁵⁵ / NICE guideline 2008 ² | Maternal hypoglycaemia | One RCT | None requiring hospital admission | NS | |
| | Caesarean section | One RCT | Caesarean section range 44–52% | NS | |
| Neonatal outcomes | | | | | |
| <i>Insulin vs glibendamide</i> | | | | | |
| Moretti 2008 ⁵⁴ | Macrosomia (birthweight >4000 g) | Seven | OR 1.07 (95% CI 0.78 to 1.47) | NS | No significant heterogeneity |
| | Birthweight (g) | Seven | WMD 20.46 g (95% CI –34.90 to 75.82) | NS | No significant heterogeneity |
| | LGA | Four | OR 1.04 (95% CI 0.75 to 1.43) | NS | No significant heterogeneity |
| | Gestational age at birth (weeks) | Four | WMD 0.02 (95% CI –0.23 to 0.26) | NS | No significant heterogeneity |
| | Neonatal hypoglycaemia | Seven | OR 1.24 (95% CI 0.91 to 1.69) | NS | No significant heterogeneity |
| | ICU admission | Four | OR 0.95 (95% CI 0.43 to 2.09) | NS | No significant heterogeneity |

| Review | Outcome | N studies | Result of meta-analysis/review | p-value | Comments |
|------------------------------|-------------------------|---|--|--|---|
| Nicholson 2009 ⁵⁵ | Neonatal hypoglycaemia | Two RCTs | Langer 2000: ⁶⁸ two consecutive BG less than 2.2 mmol/l (40 mg/dl) 6% with insulin, 9% with glibenclamide Bertini 2005: ⁶⁷ capillary glucose less than 2.2 mmol/l 4% with insulin, 33% with glibenclamide | NS in Langer 2000, ⁶⁸ significantly more infants with hypoglycaemia [capillary glucose less than 2.2 mmol/l (40 mg/dl)] with glibenclamide than with insulin in Bertini 2005 ⁶⁷ ($p=0.006$) | |
| | Hyperbilirubinaemia | Two cohort One RCT | Various definitions Serum bilirubin more than 12 mg/dl in 4–6% | NS NS | |
| | Macrosomia | Three cohort Two RCTs | Birthweight more than 4000 g: 4–7% in Langer 2000; ⁶⁸ none with insulin and 16% with glibenclamide in Bertini 2005 ⁶⁷ | NS | NS in Langer 2000, ⁶⁸ significance not reported in Bertini 2005 ⁶⁷ but more macrosomia in glibenclamide group |
| | LGA | Four cohort Two RCTs | Birthweight more than 4000 g: 8–25% in studies with NS results; Chmait 2004 ⁷⁹ 10% (should be 15%) with glibenclamide failure (i.e. insulin), 18% with glibenclamide success Percentile weight more than 90: 12–13% in Langer 2000, ⁶⁸ 4% with insulin and 25% with glibenclamide in Bertini 2005 ⁶⁷ | Conway 2004, ⁸⁰ Jacobson 2005 ⁷⁵ and Rochon 2006 ⁸³ NS; Chmait 2004 ⁷⁹ no difference found in proportion of macrosomic infants NS in Langer 2000, ⁶⁸ $p=0.073$ in Bertini 2005 ⁶⁷ | |
| | SGA | One cohort One RCT | Percentile weight more than 90: 24–25% (Criteria not reported) two (7%) in insulin group vs none in glibenclamide group | NS | Significance not reported |
| | Perinatal mortality | One cohort Two RCTs | Percentile weight less than 10: 6–7% 1% in each group in Langer 2000; ⁶⁸ none in Bertini 2005 ⁶⁷ | NS NS | |
| | Congenital malformation | One cohort One RCT | One in glibenclamide success group, none in failure group 2% in both groups | NS NS | |
| | Neonatal intensive care | One cohort One RCT | 2% in each group 6–7% NICU admission | NS NS | |
| | Birthweight | Three cohort Three RCTs Five cohort | Jacobson 2005 ⁷⁵ 24% NICU admission with insulin vs 15% with glibenclamide; NICU admission 7–10% in other studies WMD –93 g (95% CI –191 to 5) insulin vs glibenclamide Birthweight 3267–3661 g | Jacobson 2005 ⁷⁵ significantly more NICU admission in insulin group than glibenclamide group; no difference for other studies NS NS | |

| Review | Outcome | N studies | Result of meta-analysis/review | p-value | Comments |
|--|------------------------|-----------|--|---------------------------|----------|
| <i>Insulin vs metformin</i> Nicholson 2009 ⁵⁵ | Neonatal hypoglycaemia | One RCT | Any BG less than 1.6 mmol/l (28.8 mg/dl) 3.3% with metformin vs 8.1% with insulin; RR 0.41 (95% CI 0.21 to 0.78) | p=0.008 | |
| | LGA | One RCT | Percentile weight more than 90: 18.6% to 19.3% | NS | |
| | SGA | One RCT | Percentile weight less than 10: 7.2% to 9.7% | NS | |
| | Pre-term birth | One RCT | (Iatrogenic or spontaneous) 12.1% with metformin vs 7.6% with insulin | p=0.04 | |
| | Other | One RCT | Birth trauma, shoulder dystocia, 5-minute Apgar score less than 7, admission to NICU | NS | |
| | Birthweight | One RCT | 3372–3413 g | NS | |
| <i>Insulin vs acarbose</i> Nicholson 2009 ⁵⁵ / NICE guideline 2008 ² | Neonatal hypoglycaemia | One RCT | Capillary glucose less than 2.2 mmol/l (40 mg/dl) 4% with insulin, 5% with acarbose | NS | |
| | Macrosomia | One RCT | Birthweight more than 4000 g: none with insulin or acarbose | NS | |
| | LGA | One RCT | Percentile weight more than 90: 4% with insulin vs 10% with acarbose | Significance unclear | |
| | SGA | One RCT | (Criteria not reported) two (7%) in insulin group vs none in acarbose group | Significance not reported | |
| | Perinatal mortality | One RCT | None | NS | |
| | Birthweight | One RCT | Birthweight between 3194 g and 3256 g | NS | |
| Values are mean \pm SD unless indicated otherwise. | | | | | |

Appendix 4

Characteristics of primary studies

| Study | Country | Design | n | Interventions | Outcomes |
|---------------------------------|---------|----------|-------------------------|--|---|
| Glibenclamide vs insulin | | | | | |
| <i>RCT</i> | | | | | |
| Anjalakshi 2007 ⁶⁶ | India | Open RCT | G: 10 I: 13 | G: starting dose glibenclamide 0.625 mg, titrated once weekly to maintain glycaemic control I: starting dose 0.1 unit/kg body weight, increased weekly as necessary BG goal: 2-hour plasma glucose (PG) \leq 6.7 mmol/l (120 mg/dl) | Primary: unclear Maternal: glycaemic status, hypoglycaemia (not defined) Neonatal: birthweight, cord blood insulin, newborn BG |
| Bertini 2005 ⁶⁷ | Brazil | Open RCT | G: 24 A: 19 I: 27 | G: glibenclamide initial dose 5 mg in the morning, increasing every week up to 20 mg/day until achieving glucose control A: acarbose initial dose 50 mg before main meals, increasing every week in 50-mg increments up to 300 mg until achieving glucose control I: 0.7 IU/kg in first trimester, 0.8 IU/kg in second, 0.9 IU/kg in third; rapid acting human insulin (regular) before meals and NPH (isophane insulin) at bedtime in equal dosages All groups: diet and physical activity BG goal: FBG \leq 5.0 mmol/l (90 mg/dl), PPG \leq 5.6 mmol/l (100 mg/dl) | Primary: fetal hypoglycaemia, fetal weight Maternal: FPG (fasting plasma glucose), PPG, severe hypoglycaemias (necessitating hospital admission), type of delivery, weight gain Neonatal: gestational age at birth, birthweight, macrosomia ($>$ 4000 g), LGA ($>$ 90th centile), capillary BG, hypoglycaemia [capillary glucose (CG) $<$ 2.2 mmol/l (40 mg/dl)], Apgar score at 1 and 5 minutes, SGA, NICU, death, birth injuries |
| Langer 2000 ⁶⁸ | USA | Open RCT | G: 201 I: 203 | G: starting dose glibenclamide 2.5 mg orally in the morning; when indicated, dose increased by 2.5 mg the following week and by 5 mg thereafter up to 20 mg when necessary to achieve glycaemic control; mean dose 9 ± 6 mg/day I: starting dose insulin 0.7 U/kg, three times daily and increased weekly as necessary; mean dose 85 ± 48 U/day Both: standard nutritional instructions; instructed in BG monitoring BG goal: mean BG 5.0–5.9 mmol/l, FBG 3.4–5.0 mmol/l, pre-prandial BG 4.5–5.3 mmol/l, PPG less than 6.7 mmol/l | Primary: maternal glycaemic control Maternal: FBG, pre-prandial and post-prandial BG, mean BG, HbA _{1c} , adverse events, pre-eclampsia, caesarean section, hypoglycaemia (BG $<$ 2.2 mmol/l) Neonatal: gestational age at birth, birthweight, macrosomia ($>$ 4000 g), LGA ($>$ 90th percentile), SGA ($<$ 10th percentile), BG, hypoglycaemia (BG $<$ 2.2 mmol/l), respiratory distress, hyperbilirubinaemia (serum bilirubin at least 12 mg/dl (205 μ mol/l), polycythaemia (haematocrit $>$ 60%), hypocalcaemia (serum calcium \leq 7.0 mg/dl (1.8 mmol/l)), cord serum insulin |

| Study | Country | Design | n | Interventions | Outcomes |
|----------------------------------|--------------|---|------------------------------------|--|---|
| Ogunyemi 2006/7 ^{69,91} | USA | Open RCT | G: 48 I: 49 | G: glibenclamide, mean final dose 5 mg I: insulin, mean final dose NPH 30 units and regular 30 units BG goal: not reported | Primary: maternal glycaemic control, neonatal birthweight and outcomes Maternal: glucose status (only pre-enrolment glucose status), caesarean delivery, costs Child/neonatal: gestational age at delivery, birthweight, neonatal hypoglycaemia (not defined), neonatal lowest glucose level, birth defects |
| <i>Observational</i> | | | | | |
| Coetzee 1986 ⁷⁰ | South Africa | prospective cohort | G: 24 M: 59 G+M: 43 I: 39 | G: for non-obese; 5–20 mg glibenclamide M: metformin initial treatment for obese patients ($\geq 120\%$ ideal weight); 1.5–3 g metformin G+M: combination used if either agent alone failed to control BG adequately I (after G+M): switched to insulin if combination failed to control BG adequately; insulins used were soluble insulin, Insulin-Isophane, Actrapid and Monotard All groups: supervised diets BG goal: FBG < 5.5 mmol/l, PPG < 6.7 mmol/l | Primary: unclear Maternal: none Child/neonatal: perinatal mortality, LGA (high birthweight ≥ 3900 g), low birthweight (< 2500 g), hypoglycaemia (< 1.4 mmol/l), jaundice (needing phototherapy), congenital abnormalities |
| Duncan 2005 ⁷¹ | USA | Retrospective cohort (chart review) | G: 28 I: 62 | G: glibenclamide I: insulin BG goal: not reported | Primary: unclear Maternal: pre-eclampsia, labour induction, caesarean section Neonatal: gestational age at delivery, macrosomia |
| Fines 2003 ⁷² | USA | Retrospective case-control (retrospective cohort) | G: 40 I: 44 | G: glibenclamide I: insulin BG goal: not reported | Primary: unclear Maternal: none Neonatal: gestational age at delivery, Apgar scores, birthweight, macrosomia (> 4000 g), ponderal index, NICU admission |
| Gilson 2002 ⁷³ | USA (Alaska) | Prospective cohort | G: 11 I: 11 | G: glibenclamide I: insulin Both groups: diet and intensive monitoring BG goal: FBG < 5.3 mmol/l, 2-hour PPG < 6.7 mmol/l | Primary: unclear Maternal: maternal glycaemic control, shoulder dystocia Neonatal: hypoglycaemia (< 2.2 mmol/l), LGA (> 90 th percentile), macrosomia (> 4000 g), birth complications |
| Goodman 2008 ⁷⁴ | USA | Retrospective cohort | G: 150 I: 175 | G: glibenclamide I: insulin BG goal: not reported | Primary: primary caesarean delivery rate Maternal: maternal complications Neonatal: fetal and neonatal complications, birthweight > 4500 g |

| Study | Country | Design | n | Interventions | Outcomes |
|------------------------------|---------|--|------------------|---|---|
| Holt 2008 ⁵² | UK | Prospective cohort | G: 44 I: 45 | G: glibenclamide starting dose 2.5–5 mg depending on weight and degree of hyperglycaemia, maximum dose 15 mg/day; median dose 5 mg (range 2.5–15 mg) I: insulin; type and dose of insulin as per clinician's choice Both groups: lifestyle modification, glucose monitoring BG goal: were FBG 6.0 mmol/l, and PPG 7.0 mmol/l | Primary: unclear Maternal: caesarean section Neonatal: gestational age at delivery, neonatal jaundice (hyperbilirubinaemia requiring phototherapy), neonatal hypoglycaemia (≤ 2.6 mmol/l), respiratory distress (requiring admission to NICU), birthweight, birth centile, macrosomia (> 4000 g), Apgar 1 and 5 minutes, NICU admission |
| Jacobson 2005 ⁷⁵ | USA | Retrospective cohort (Kaiser Permanente, North California) | G: 236 I: 268 | G: initial daily dose of 2.5 mg with morning meal, if glycaemic goal not met, increased by 2.5 mg initially and thereafter by 5 mg weekly; if dose exceeded 10 mg daily, twice daily dosing was considered up to maximum dose of 20 mg/day; maximum daily glibenclamide dose 5.6 ± 4.6 mg (median 5, range 1.25–20 mg) I: mean daily insulin dose 34.4 ± 28.1 units (median 28, range 2–242 units) Both groups: nutritional counselling; instruction in BG meter use BG goal: FPG 5.6 mmol/l (100 mg/dl), 1-hour PPG 8.6 mmol/l (155 mg/dl), 2-hour PPG 7.2 mmol/l (130 mg/dl) | Primary: unclear Maternal: caesarean section, pre-eclampsia, mode of delivery, maternal hypoglycaemia (< 60 mg/dl) Neonatal: preterm delivery (< 37 weeks), LGA (> 90 th percentile), SGA (< 10 th percentile), birthweight, macrosomia (≥ 4000 g), hyperbilirubinaemia (bilirubin ≥ 12 mg/dl), polycythaemia (haematocrit $\geq 60\%$), hypocalcaemia (calcium < 7.0 mg/dl), neonatal hypoglycaemia (based on discharge coding), congenital anomalies, birth injuries, phototherapy, NICU admission, gestational age at delivery |
| Langer 2006 ⁷⁶ | USA | Cohort study | G: 210 I: 175 | G: glibenclamide I: insulin BG goal: mean BG < 5.6 mmol/l | Primary: adverse pregnancy outcome (LGA/macrosomia, metabolic and respiratory complications, ICU admission, caesarean delivery) Maternal: caesarean section Neonatal: LGA/macrosomia, metabolic and respiratory complications, ICU admission |
| Patterson 2008 ⁷⁷ | USA | Retrospective cohort | G: 59 I: 40 | G: glibenclamide I: insulin BG goal: not reported | Primary: not reported Maternal: operative delivery, pre-eclampsia, post-partum haemorrhage, third and fourth degree perineal lacerations, intrapartum infections Neonatal: macrosomia, 1- and 5-minute Apgar scores, preterm delivery |

| Study | Country | Design | n | Interventions | Outcomes |
|---|-------------|--|--------------------------------|--|--|
| Ramos 2007 ⁶¹ | USA | Retrospective cohort (Kaiser Permanente, North California) | G: 44 I: 78 | G: maximum daily glibenclamide dose 8.2 ± 5.6 mg (median 5, range 2.5–20 mg) I: mean daily insulin dose 47.1 ± 36.8 units (median 74, range 1–242 units) Both groups: nutritional counselling; instruction in BG meter use BG goal: FPG 5.6 mmol/l (100 mg/dl), 1-hour PPG 8.6 mmol/l (155 mg/dl), 2-hour PPG 7.2 mmol/l (130 mg/dl) | Primary: unclear Maternal: caesarean section, pre-eclampsia Neonatal: preterm delivery (<37 weeks), LGA (>90th percentile), SGA (<10th percentile), birthweight, macrosomia (≥ 4000 g), hyperbilirubinaemia (bilirubin ≥ 12 mg/dl), polycythaemia (haematocrit $\geq 60\%$), hypocalcaemia (calcium <7.0 mg/dl), neonatal hypoglycaemia (based on discharge coding), congenital anomalies, birth injuries, phototherapy, NICU admission, gestational age at delivery |
| Yogev 2004 ⁷⁸ | USA, Israel | Prospective cohort | G: 25 I: 30 | G: glibenclamide starting dose 2.5 mg orally in the morning; if necessary increased by 2.5 mg the following week and 5 mg thereafter up to 20 mg; mean dose 8 ± 4 mg/day I: insulin started at 0.7 U/kg/day given three times daily, dose adjusted weekly if necessary; NPH and rapid acting; mean dose 72 ± 23 U/kg/day Both groups: diet therapy, continuous glucose monitoring system BG goal: mean BG ≤ 5.3 mmol/l (95 mg/dl), FBG 3.3–5.0 mmol/l (60–90 mg/dl), PPG ≤ 6.7 mmol/l (120 mg/dl) | Primary: maternal hypoglycaemia (BG <2.8 mmol/l (50 mg/dl); symptomatic, significant, or asymptomatic, defined), maternal mean BG Maternal: mean BG Neonatal: none |
| Glibenclamide failure (predictors) | | | | | |
| Chmait 2004 ⁷⁹ | USA | Prospective cohort | G success: 56 G failure: 13 | G success: glibenclamide started at 2.5–5.0 mg/day, increased if necessary in 2.5–5.0 mg increments to a maximum of 20 mg/day (10 mg twice a day) G failure: for those discontinuing glibenclamide, insulin 0.7 U/kg at 1–18 weeks' gestation, 0.8 U/kg 18–26 weeks' gestation, 0.9 U/kg 26–36 weeks' gestation, 1 U/kg 36–40 weeks' gestation; for those continuing glibenclamide and adding insulin, dose was adjusted every 2 weeks Both groups: taught dietary therapy and capillary glucose monitoring, individual nutritional counselling BG goal: FBG values ≤ 5.0 mmol/l (90 mg/dl) and 1-hour PPG ≤ 7.2 mmol/l (130 mg/dl) | Primary: unclear Maternal: baseline characteristics, medical and obstetric history, delivery outcomes, caesarean section, shoulder dystocia Neonatal: birthweight, macrosomia (birthweight >4000 g), neonatal hypoglycaemia [BG <2.2 mmol/l (40 mg/dl)], hyperbilirubinaemia (bilirubin >15 mg/dl), polycythaemia (haematocrit >60%), hypocalcaemia (serum calcium <8.0 mg/dl) |

| Study | Country | Design | n | Interventions | Outcomes |
|----------------------------|---------|----------------------------|--------------------------------|---|---|
| Conway 2004 ⁸⁰ | USA | Retrospective cohort | G success: 63 G failure: 12 | G success: glibenclamide initial dose 2.5 mg in the morning (in some cases at bedtime); dose increased as needed but not more frequently than every 3 days; up to maximum of 20 mg (10 mg morning, 10 mg evening) G failure: insulin starting dose 0.7 to 1.0 U/kg Both groups: medical nutrition therapy, glucose meter BG goal: FBG \leq 5.3 mmol/l (95 mg/dl), 2-hour PPG \leq 6.4 mmol/l (115 mg/dl), overall mean BG 5.8 mmol/l (105 mg/dl) | Primary: unclear Maternal: baseline characteristics [maternal age, parity, relatives with diabetes mellitus (DM), previous gestational diabetes mellitus (GDM), previous macrosomia, baseline glucose status] Neonatal: birthweight, macrosomia, neonatal hypoglycaemia (requiring glucose infusions) |
| Kahn 2006 ⁶³ | USA | Retrospective cohort | G success: 77 G failure: 18 | G success: initial dose of glibenclamide individualised based on weight and patient's degree of hyperglycaemia; instructed to take glibenclamide 30 minutes before breakfast and dinner; maximum dose 10 mg twice daily G failure: insulin, no details Both groups: diet counselling, taught to test their own glucose levels BG goal: FBG $<$ 5.3 mmol/l (95 mg/dl), 1-hour PPG $<$ 7.8 mmol/l (140 mg/dl) | Primary: glibenclamide failure Maternal: pre-eclampsia, maternal hypoglycaemia, delivery route, birthweight, dystocia, demographic details Neonatal: neonatal complications, NICU, respiratory distress syndrome, neonatal hypoglycaemia [BG $<$ 2.2 mmol/l (40 mg/dl)], LGA ($>$ 90th percentile), macrosomia ($>$ 4000 g) |
| Langer 2006 ⁸¹ | USA | Cohort study | Total: 379 | Glibenclamide treatment BG goal: mean BG $<$ 5.6 mmol/l, post-meal BG $<$ 6.7 mmol/l | Primary: achievement of desired level of glycaemic control (mean BG $<$ 5.6 mmol/l, post-meal BG $<$ 6.7 mmol/l) Maternal: glibenclamide dose, GDM severity (defined by FPG levels), ethnicity, maternal age, obesity, previous GDM, gestational age at diagnosis, parity Neonatal: none |
| Parrish 2008 ⁸² | USA | Retrospective cohort study | G success: 44 G failure: 14 | Glibenclamide treatment BG goal: not reported | Primary: glibenclamide failure Maternal: gestational age at diagnosis and initiation of treatment, personal history of gestational diabetes, first degree relative with diabetes, caesarean delivery Neonatal: neonatal outcomes |

| Study | Country | Design | n | Interventions | Outcomes |
|--------------------------------------|---------------------------|----------------------|--------------------------------|--|---|
| Rochon 2006 ⁸³ | USA | Retrospective cohort | G success: 80 G failure: 21 | G success: initial dose of glibenclamide 2.5–5 mg per day and titrated in 5-mg increments weekly as needed to a maximum of 10 mg twice a day (20 mg/day) G failure: standard weight-based human insulin regimen, given as a combination of NHP and regular insulin three times daily; glibenclamide discontinued Both groups: diabetes teaching (BG monitoring, dietary counselling); self-management plan BG goal: FBG 3.3–5.0 mmol/l (60–90 mg/dl), 2-hour PPG ≤ 6.7 mmol/l (120 mg/dl) | Primary: unclear Maternal: demographic information, glycaemic control, caesarean delivery Neonatal: gestational age at delivery, preterm delivery, birthweight, macrosomia, shoulder dystocia, 5-minute Apgar <7, NICU admission, hypoglycaemia (≤ 2.2 mmol/l, requiring NICU admission) |
| Velazquez 2003 ⁸⁴ | USA | Prospective cohort | G success: 31 G failure: 7 | G: glibenclamide (maximum 20 mg/day) I: insulin BG goal: FBG ≤ 5.8 mmol/l, 2-hour PPG ≤ 6.7 mmol/l | Primary: unclear Maternal: successful glycaemic control, caesarean delivery Neonatal: LGA |
| Metformin vs insulin | | | | | |
| <i>RCT</i> | | | | | |
| Hague 2003 ⁸⁵ (MiG pilot) | Australia/ New Zealand | Open RCT | M: 16 I: 14 | M: metformin I: insulin BG goal: not reported | Primary: unclear Maternal: caesarean section, pre-eclampsia, induction of labour Neonatal: gestational age at delivery, birthweight, jaundice, phototherapy, cord glucose, cord C-peptide, time in special care nursery |
| Moore 2007 ⁸⁶ | USA | Open RCT | M: 32 I: 31 | M: initial dose of oral metformin 500 mg twice a day, increased as necessary to maintain glucose control (max. 1000 mg twice a day); 27/32 achieved glucose homeostasis on the starting dose I: patients started at 0.7 units of insulin per kg bodyweight injected twice daily to maintain euglycaemia; total daily dose split: 2/3 in the morning, 1/3 before evening meal; combination of regular insulin and NPH Both groups: dietary instruction by a registered dietician; instruction from a nurse educator; portable glucose meter BG goal: FBG 3.3–5.0 mmol/l (60–90 mg/dl); 2-hour post-prandial 6.7 mmol/l (< 120 mg/dl) | Primary: fasting and 2-hour glucose assessments, mode of delivery, shoulder dystocia, postpartum haemorrhage Maternal: fasting and 2-hour glucose assessments, mode of delivery, shoulder dystocia, postpartum haemorrhage Neonatal: hypoglycaemia [BG < 2.2 mmol/l (40 mg/dl)], hyperbilirubinaemia (serum bilirubin > 5 mg/dl), fetal weight, respiratory distress syndrome, NICU admission, fetal/neonatal death |

| Study | Country | Design | n | Interventions | Outcomes |
|---|---------------------------|---|------------------|--|--|
| Rowan 2007/8 (MiG) ^{88,88} | Australia/ New Zealand | Open RCT | M: 363 I: 370 | M: metformin started at a dose of 500 mg once or twice daily with food and increased (over period of 1–2 weeks) to meet glycaemic targets up to a maximum daily dose of 2500 mg; if targets not achieved on metformin alone, insulin was added; median daily dose 2500 mg (range 1750–2500 mg) I: insulin prescribed according to usual practice, maximum daily dose 50 units Both groups: lifestyle intervention (diet and exercise), BG monitoring BG goal: BG after overnight fast < 5.5 mmol/l; 2-hour PPG < 7.0 mmol/l | Primary: composite of neonatal complications (neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5-minute Apgar < 7, premature birth) Maternal: maternal hypertensive complications, glycaemic control, preferences, adverse events Neonatal: hypoglycaemia (BG < 2.6 mmol/l), hyperbilirubinaemia (serum bilirubin > 5 mg/dl), birthweight, respiratory distress, NICU admission, perinatal death, congenital anomalies |
| <i>Observational</i> Balani 2008 ⁸⁹ | UK | Prospective cohort | M: 80 I: 80 | M: metformin 500 mg twice a day titrated up to a maximum of 2500 mg/day to achieve target home blood glucose monitoring values I: basal-bolus human insulin BG goal: FBG < 6 mmol/l, 1-hour PPG < 8 mmol/l, 2-hour PPG < 7 mmol/l | Primary: not reported Maternal: maternal weight gain, hypertension, pre-eclampsia, caesarean delivery, abnormalities in post-natal glucose tolerance test Neonatal: prematurity, jaundice, NICU admissions, birthweight, macrosomia, shoulder dystocia, congenital malformations or abnormalities |
| Tertti 2008 ⁵⁶ | Finland | Retrospective cohort, matched for BMI and age | M: 45 I: 45 | M: initial dose of metformin between 500 mg once a day and 750 mg twice a day; mean dose 1 g/day I: insulin treatment usually started with intermediate-acting insulin; 13 patients treated with short-acting insulin, nine with intermediate-acting, 23 with both short- and intermediate-acting Both groups: dietary counselling BG goal: FBG < 5.5 mmol/l, PPG < 7.8 mmol/l | Primary: unclear Maternal: pregnancy-induced hypertension, pre-eclampsia, mode of delivery, shoulder dystocia Neonatal: birthweight, macrosomia, SGA, prematurity, 5-minute Apgar score, umbilical artery pH < 7.05 and base excess, hypoglycaemia (PG < 2.6 mmol/l during first 2 hours), hyperbilirubinaemia (need for phototherapy), need for intensive care treatment, respiratory distress syndrome |

Values are mean ± SD unless indicated otherwise.

Appendix 5

Characteristics of participants in primary studies

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|---------------------------------|---|--|---|--|-------------------------|---|--|---|
| Glibenclamide vs insulin | | | | | | | | |
| <i>RCT</i> | | | | | | | | |
| Anjalakshi 2007 ⁶⁶ | G: 24.9 ± 3.73 years I: 27.46 ± 5.83 years | Not reported | G: 22.82 ± 3.5 kg/m ² I: 25.32 ± 5.14 kg/m ² | Indian (presumably) | Not reported | G: 22.5 ± 4.72 weeks I: 22.62 ± 5.62 weeks | Singleton pregnancies Diagnosis: 75-mg OGTT, GDM diagnosed based on WHO criteria of 2-hour PG > 7.8 mmol/l (140 mg/dl) Included if after 2 weeks of medical nutrition therapy 2-hour PG remained ≥ 6.7 mmol/l (120 mg/dl) | G: 2-hour PG 9.3 ± 1.27 mmol/l; HbA _{1c} 5.48 ± 0.79% I: 2-hour PG 9.71 ± 1.72 mmol/l; HbA _{1c} 5.75 ± 1.23% |
| Bertini 2005 ⁶⁷ | G: 31.2 ± 4.5 years A: 31.5 ± 5.8 years I: 28.7 ± 6.0 years | G: 3.2 ± 6.5 pregnancies A: 2.9 ± 1.6 pregnancies I: 2.5 ± 1.6 pregnancies | G: 27.5 ± 5.8 kg/m ² A: 25.7 ± 4.2 kg/m ² I: 27.0 ± 7.2 kg/m ² | Not reported | Not reported | At diagnosis range 11–33 weeks | Singleton pregnancies Diagnosis: FPG and 75-mg OGTT, GDM diagnosed based on WHO/Brazilian Health Ministry criteria of FPG ≥ 6.1 mmol/l (110 mg/dl) and OGTT 2-hour PG ≥ 7.8 mmol/l (140 mg/dl) Included if after 3 days diet and exercise FPG was > 5.0 mmol/l (90 mg/dl) and PPG was > 5.6 (100 mg/dl) | Not reported |
| Langer 2000 ⁶⁸ | G: 29 ± 7 years I: 30 ± 6 years | G: 28% nulliparous I: 29% nulliparous | ≥ 27.3 kg/m ² Before pregnancy G: 70% I: 65% | 83% Hispanic, 12% non-Hispanic white, 5% black | G: 43% I: 45% | G: 24 ± 7 weeks I: 25 ± 7 weeks | Singleton pregnancies 11–33 weeks of gestation At least 7.3 mmol/l on 50-g OGCT 100-g OGTT; included if FPG at least 5.3 mmol/l and less than 7.8 mmol/l If FPG less than 5.3 mmol/l, initially treated with diet, but enrolled in the study if FPG was at least 5.3 mmol/l or PPG was at least 6.7 mmol/l | G: FPG 5.8 ± 1.4 mmol/l; PPG 7.2 ± 1.4 mmol/l, HbA _{1c} 5.7 ± 1.3% I: FPG 6.0 ± 1.4 mmol/l; PPG 7.16 ± 1.5 mmol/l, HbA _{1c} 5.6 ± 1.2% |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|-----------------------------|---|--------------|--|---|-------------------------|--|--|---|
| Ogunyemi 2007 ⁶⁹ | Not reported | Not reported | G: 32.0 ± 7.6 kg/m ² I: 30.8 ± 6.9 kg/m ² | 80% Hispanic, 15% African American | Not reported | G: 28.1 ± 7.6 weeks I: 24.6 ± 8.0 weeks, <i>p</i> = 0.039 | Not reported | HbA _{1c} G: HbA _{1c} 5.8 ± 0.7%, I: HbA _{1c} 7.5 ± 1.7% (<i>p</i> = 0.001) OGTT fasting G: 5.76 ± 1.12 mmol/l, I: 6.43 ± 1.09 mmol/l (<i>p</i> = 0.014) OGTT 2-hour G: 9.93 ± 1.93 mmol/l, I: 10.94 ± 2.33 mmol/l (<i>p</i> = 0.053) |
| <i>Observational</i> | | | | | | | | |
| Coetzee 1986 ⁷⁰ | 38% ≥ 35 years | Not reported | 70% ≥ 120% ideal weight | Not reported | Not reported | Not reported | GDM diagnosed if and two of three criteria were exceeded on two separate OGTTs using 50-g glucose: (1) FBG 5.5 mmol/l, (2) maximum levels 10 mmol/l, (3) 2-hour level 7.0 mmol/l | Not reported |
| Duncan 2005 ⁷¹ | No significant difference (no data given) | Not reported | G: 32% morbidly obese (BMI > 40 kg/m ²) I: 33% morbidly obese | No significant difference (no data given) | Not reported | Not reported | Singleton pregnancies Women with gestational diabetes requiring medical therapy | Not reported |
| Fines 2003 ⁷² | Not reported | Not reported | Not reported | Not reported | Not reported | Unclear, at least 4 weeks prior to delivery | Not reported | Not reported |
| Gilson 2002 ⁷³ | Not reported | Not reported | 91% > 28 kg/m ² | American Indian/ Alaska Native | Not reported | Not reported | Women with GDM unable to maintain glycaemic control (FBG < 5.3 mmol/l, 2-hour PPG < 6.7 mmol/l) with diet and intensive monitoring could chose between insulin and glibenclamide | Not reported |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|-----------------------------|--|--|--|--|-------------------------|--|--|---|
| Goodman 2008 ⁷⁴ | No significant difference (no data given) | Not reported | Not reported | Majority were Hispanic and indigent | Not reported | Not reported | Women with gestational diabetes failing diet therapy | Not reported |
| Holt 2008 ⁵² | G: 33.4 ± 6 years I: 33.4 ± 4.7 years | G: 45% multiparous, 41% primiparous I: 27% multiparous, 62% primiparous | G: 29.8 ± 5.3 kg/m ² I: 33.9 ± 8.7 kg/m ² p = 0.011 | G: 48% European, 52% Asian I: 80% European, 20% Asian p = 0.002 | Not reported | 31 weeks (range 21–37 weeks) | Women at risk of developing GDM (defined) were given OGTT; GDM was diagnosed according to WHO criteria (FPG ≥ 7.0 mmol/l), 2-hour BG ≥ 7.8 mmol/l Dietary and lifestyle modifications according to Diabetes UK guidelines; target BG were FBG 6.0 mmol/l, and PPG 7.0 mmol/l; if two readings greater than target values, offered pharmacological treatment – women could chose between glibenclamide and insulin | G: FBG 6.3 ± 1.3 mmol/l; 2-hour BG 10.9 ± 2.7 mmol/l; HbA _{1c} 6.4 ± 0.7% I: FBG 5.8 ± 0.7 mmol/l; 2-hour BG 9.5 ± 2.7 mmol/l; HbA _{1c} 5.8 ± 0.7% p < 0.05 for all |
| Jacobson 2005 ⁵⁵ | G: 32.8 ± 5.4 years I: 32.1 ± 5.2 years | Nulliparous G: 33% I: 34% | G: 30.6 ± 7.0 kg/m ² ; BMI ≥ 30 kg/m ² 47% I: 31.9 ± 6.8 kg/m ² p = 0.04; BMI ≥ 30 kg/m ² 55% | G: white 28%, Hispanic 24%, black 4%, Asian 37% I: white 43%, Hispanic 25%, black 4%, Asian 24%, p = 0.001 | G: 58% I: 55% | G: 30.3 ± 4.5 weeks I: 30.4 ± 4.8 weeks | Singleton pregnancies Abnormal 50-g glucose load test ≥ 7.8 mmol/l (140 mg/dl) Diagnostic 3-hour OGTT using National Diabetes Data Group criteria (FBP ≥ 5.8, 1-hour ≥ 10.5, 2-hour ≥ 9.2, 3-hour 8.0 mmol/l); excluded if FPG ≥ 7.8 mmol/l on OGTT Insulin group diagnosed 1999 to 2000, glibenclamide group diagnosed 2001 to 2002 | G: FBG 5.68 ± 0.79 mmol/l; OGCT 1-hour 9.76 ± 1.47 mmol/l I: FBG 5.85 ± 0.72 mmol/l, p = 0.005; OGCT 1-hour 9.94 ± 1.45 mmol/l |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|------------------------------|---|--|---|---|-------------------------|--|---|---|
| Langer 2006 ⁷⁶ | Not reported | Not reported | Not reported; women were overweight or obese | Not reported | Not reported | Not reported | Overweight (BMI 26–29 kg/m ²) or obese (BMI >30 kg/m ²) women with GDM treated with glibenclamide or insulin Included if targeted level of glycaemic control (mean BG <5.6 mmol/l) was achieved | Not reported |
| Patterson 2008 ⁷⁷ | No significant difference (no data reported) | No significant difference in parity or gavidity (no data reported) | Not reported | Not reported | Not reported | Not reported | Singleton pregnancies between 24 weeks of gestation with A2 gestational diabetes with women taking glibenclamide or insulin | Not reported |
| Ramos 2007 ⁶¹ | G: 35.2 ± 4.7 years I: 31.5 ± 5.8 years p < 0.001 | Nulliparous G: 30% I: 44% | G: 29.1 ± 5.8 kg/m ² ; BMI ≥ 30 kg/m ² 30% I: 32.4 ± 6.4 kg/m ² p = 0.003; BMI ≥ 30 kg/m ² 59%, p = 0.006 | G: white 16%, Hispanic 18%, black 7%, Asian 50% I: white 19%, Hispanic 32%, black 13%, Asian 26% | G: 77% I: 88% | G: 27.5 ± 6.1 weeks I: 26.9 ± 6.8 weeks | Singleton pregnancies 50-g OGCT ≥ 11.1 mmol/l (200 mg/dl) and FPG ≥ 5.8 mmol/l (105 mg/dl) Insulin group diagnosed 1999–2000, glibenclamide group diagnosed 2001–2 | G: FBG 6.58 ± 0.62 mmol/l, OGCT 1-hour 12.35 ± 1.25 mmol/l I: FBG 6.64 ± 0.56 mmol/l, OGCT 1-hour 12.8 ± 1.38 mmol/l |
| Velazquez 2003 ⁸⁴ | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | GDM not controlled with diet | Not reported |
| Yogev 2004 ⁷⁸ | G: 28.3 ± 3.3 years I: 28.1 ± 3.9 years | Nulliparous G: 28% I: 27% | G: 27.5 ± 2.1 kg/m ² , 48% obese I: 27.6 ± 3.1 kg/m ² , 50% obese | Not reported | Not reported | G: 33.0 ± 2.8 weeks I: 33.4 ± 3.9 weeks | Women with singleton pregnancies after 24 weeks of gestation without any known fetal malformations Patients with > 7.2 mmol/l (130 mg/dl) on 50-g glucose challenge test underwent 3-hour 100-g OGTT; assigned to pharmacological therapy if FBG on OGTT was > 5.3 mmol/l (95 mg/dl) | G: FBG 5.4 ± 1.5 mmol/l I: FBG 5.5 ± 1.3 mmol/l |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|---|---|---|---|---|---|---|---|--|
| Glibenclamide failure (predictors) | | | | | | | | |
| Chmait 2004 ⁷⁹ | G success: 32 ± 5 years G failure: 31 ± 7 years p = 0.017 | Nulliparity G success: 14.3% G failure: 7.7% | Weight G success: 82 ± 15 kg G failure: 92 ± 25 kg | G success: 91% Hispanic, 9% non-Hispanic G failure: 69% Hispanic, 31% non-Hispanic | G success: 46% G failure: 45% | G success: 29.7 ± 6.6 weeks G failure: 23 ± 6.9 weeks p = 0.002 | 13 to 38 weeks of gestation Patients with 7.8–11.1 mmol/l (140–200 mg/dl) on 1-hour 50-g OGTT underwent 100-g OGTT; GDM was diagnosed if BG of 1-hour OGTT was > 11.1 mmol/l (200 mg/dl) or if two or more of the 100-g OGTT values were abnormal according to the Carpenter and Coustan criteria Dietary therapy for 1 week, medical management initiated if at least 20% of weekly FBG values > 5.0 mmol/l (90 mg/dl) and 1-hour PPG > 7.2 mmol/l (130 mg/dl), women given choice of glibenclamide or insulin (all chose glibenclamide) | G success: FBG 5.2 ± 0.83 mmol/l; 2-hour OGTT 9.4 ± 1.7 mmol/l G failure: FBG 5.83 ± 1.2 mmol/l; 2-hour OGTT 10.7 ± 1.4 mmol/l |
| Conway 2004 ⁸⁰ | G success: 31.3 ± 6.1 years G failure: 30.3 ± 5.0 years | Living children G success: 1.8 ± 1.7 G failure: 2.2 ± 1.8 | 33.1 kg/m ² (range 19.4–56.8 kg/m ²); no significant difference between groups | Not reported | First degree relative with DM G success: 73.0% G failure: 83.3% | G success: 20.0 ± 8.3 weeks G failure: 18.4 ± 8.4 weeks | Diagnosis of GDM according to ADA guidelines If within 2 weeks of medical nutrition therapy glycaemic control was not achieved, offered glibenclamide as an alternative to insulin initiation if gestational age 11–33 weeks, FBG on OGTT < 7.8 mmol/l (140 mg/dl) and no allergy to sulphonamide drugs | G success: FBG 5.7 ± 0.8 mmol/l; 2-hour OGTT 9.4 ± 1.9 mmol/l G failure: FBG 6.4 ± 1.3 mmol/l; 2-hour OGTT 11.3 ± 3.7 mmol/l p < 0.02 for both |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|----------------------------|---|---|---|---|---|---|--|---|
| Kahn 2006 ⁶³ | G success: 29 ± 5 years G failure: 34 ± 5 years p = 0.001 | Gravidity G success: 2.7 ± 1.6 G failure: 4.3 ± 2.7 p = 0.01 Parity G success: 1 ± 1 G failure: 2 ± 1.7 p = 0.03 | Overall 73% overweight or obese G success: 30 ± 6 kg/m ² G failure: 32 ± 8 kg/m ² | 53% Hispanic, 32% non-Hispanic white, 8% African American, 5% other ethnicities | Not reported | G success: 31 ± 4 weeks G failure: 24 ± 7 weeks p = 0.001 | Singleton pregnancies GDM diagnosed according to Carpenter and Coustan criteria: at least two abnormal values on a diagnostic 100-g 3-hour OGTT (FBG ≥ 5.3 mmol/l, 1-hour ≥ 10.0 mmol/l, 2-hour ≥ 8.6 mmol/l, 3-hour ≥ 7.8 mmol/l); also women with ≥ 11.1 mmol/l on 50-g glucose challenge and FBG ≥ 5.3 mmol/l Patients considered to fail diet therapy if after about 2 weeks, 20% of FBG were ≥ 5.3 mmol/l or 1-hour PPG were ≥ 7.8 mmol/l | G success: FBG 5.6 ± 0.9 mmol/l G failure: FBG 6.2 ± 1.3 mmol/l p = 0.045 |
| Langer 2006 ⁸¹ | Not reported | Not reported | Not reported | Not reported | Not reported | Not reported | Women with GDM treated with glibenclamide | Not reported |
| Parrish 2008 ⁸² | Not reported | Not reported | Not reported | Not reported | First degree relative G success: 66% G failure: 93% p = NS | G success: 19 weeks G failure: 28 weeks p < 0.001 | Women with gestational diabetes treated with glibenclamide | Not reported |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|--------------------------------------|--|--|--|--|--|--|--|---|
| Rochon 2006 ⁸³ | G success: 30.5 ± 5.8 years G failure: 31.3 ± 6.2 years | Multiparous G success: 70% G failure: 86% | G success: 31.5 ± 7.5 kg/m ² G failure: 32.2 ± 5.0 kg/m ² | G success: 59% Hispanic, 30% black, 10% Asian, 1% white G failure: 57% Hispanic, 29% black, 10% Asian, 5% white | G success: 52% G failure: 14% <i>p</i> = 0.076 | G success: 26 ± 7 weeks G failure: 24 ± 7 weeks | 50-g oral glucose challenge test for screening, if 1-hour value ≥ 7.5 mmol/l (135 mg/dl), 100-g 3-hour OGTT done; GDM diagnosed according to Carpenter and Coustan criteria: at least two abnormal values on a OGTT (FBG ≥ 5.3 mmol/l, 1-hour ≥ 10.0 mmol/l, 2-hour ≥ 8.6 mmol/l, 3-hour ≥ 7.8 mmol/l) Trial of diet for at least a week, if glycaemic goals not met, switched to glibenclamide | G success: FBG 5.7 ± 1.2 mmol/l; 2-hour OGTT 9.9 ± 1.8 mmol/l G failure: FBG 5.9 ± 0.8 mmol/l; 2-hour OGTT 10.5 ± 2.6 mmol/l |
| Metformin vs insulin | | | | | | | | |
| <i>RCT</i> | | | | | | | | |
| Hague 2003 ⁸⁵ (MIG pilot) | M: 33.7 ± 4.44 years I: 34.1 ± 3.70 years | M: median I (range 0–4) I: median I (range 0–5) | M: 39.5 ± 6.94 kg/m ² I: 37.9 ± 6.87 kg/m ² | Not reported | Not reported | M: 29.8 ± 4.49 weeks I: 30.4 ± 4.67 weeks | Gestational diabetes diagnosed according to criteria of Australasian Diabetes in Pregnancy Society; no more details | M: FBG 5.6 ± 1.26 mmol/l; 2-hour BG 10.0 ± 2.07 mmol/l I: FBG 5.4 ± 0.52 mmol/l; 2-hour BG 9.4 ± 1.42 mmol/l |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|-------------------------------------|--|--|---|--|-------------------------|--|--|--|
| Moore 2007 ⁸⁶ | M: 27.1 ± 4.7 years I: 27.7 ± 6.7 years | Parity M: 1.4 ± 1.3 I: 2.3 ± 2.3 | M: weight 104.28 ± 25.45 kg; BMI 39.7 ± 9.0 kg/m ² I: 67.49 ± 19.5 kg; BMI: 35.3 ± 6.7 kg/m ² p = 0.01 for weight p = 0.045 for BMI | M: 20 (63%) African American, 11 (34%) Native American, 1 (3%) Caucasian I: 11 (35%) African American, 17 (54%) Native American, three (10%) Caucasian | Not reported | M: 27.8 ± 6.5 weeks I: 28.9 ± 5.0 weeks | Women with 1-hour glucose challenge test (50-g) levels of 7.8 mmol/l (140 mg/dl) or above then received a 3-hour glucose tolerance test GMD diagnosed according to ADA levels (5.8, 10.5, 9.2 and 8.0 mmol/l for fasting, 1-, 2-, 3-hour glucose) | Not reported |
| Rowan 2007/8 ^{87,88} (MIG) | M: 33.5 ± 5.4 years I: 33.0 ± 5.1 years | Nulliparous M: 31.7% I: 31.9% | M: 32.2 ± 8.2 kg/m ² I: 31.9 ± 7.6 kg/m ² (Early pregnancy) | M: 48.2% European/white, 20.1% Polynesian, 10.5% Indian, 13.5% Chinese/south-east Asian, 7.7% other/mixed I: 45.4% European/White, 22.4% Polynesian, 14.9% Indian, 10.0% Chinese/south-east Asian, 7.3% other/mixed | M: 44.6% I: 48.9% | M: 30.2 ± 3.3 weeks I: 30.1 ± 3.2 weeks | 18–45 years, singleton pregnancies, 20–33 weeks' gestation Diagnosis of GDM according to criteria of the Australasian Diabetes in Pregnancy Society After lifestyle intervention (diet and exercise) more than one capillary BG value > 5.4 mmol/l after overnight fast or more than one 2-hour PPG measurement > 6.7 mmol/l | M: OGTT FBG 5.7 ± 1.2 mmol/l, 2-hour OGTT 9.7 ± 2.1 mmol/l, HbA _{1c} 5.7 ± 0.6% I: OGTT FBG 5.7 ± 1.1 mmol/l, 2-hour OGTT 9.39 ± 2.1 mg/dl, HbA _{1c} 5.8 ± 0.7% |
| Observational | Not reported | Not reported | Not reported (groups matched for BMI) | Not reported (groups matched for ethnicity) | Not reported | Not reported | Women with gestational diabetes not adequately controlled by dietary measures | Not reported |
| Balani 2008 ⁸⁹ | Not reported | Not reported | Not reported (groups matched for BMI) | Not reported (groups matched for ethnicity) | Not reported | Not reported | Women with gestational diabetes not adequately controlled by dietary measures | Not reported |

| Study | Age | Parity, etc. | BMI | Ethnicity | Diabetes family history | Gestational age at start of therapy | Diagnostic criteria for inclusion (and dietary failure) | Initial glucose status |
|---------------------------|--|---|--|----------------|------------------------------------|--|--|---|
| Tertti 2008 ⁵⁶ | M: 32.8 ± 5.0 years I: 32.7 ± 4.7 years | Primipara M: 22% I: 42% p = 0.05 | M: 34.0 ± 6.4 kg/m ² I: 33.2 ± 6.2 kg/m ² | 91% Caucasians | No details; classified 'high risk' | M: 24.8 ± 5.5 weeks I: 24.3 ± 5.7 weeks | Singleton pregnancies 2-hour 75-g OGTT because considered to be high risk; criteria for GDM at least two of three abnormally high values in 75-g OGTT (FBG ≥ 4.8, 1-hour ≥ 10, 2-hour ≥ 8.7 mmol/l) Dietary counselling; pharmacological treatment started if after 1 week FPG was ≥ 5.5 mmol/l at least twice or FPG was ≥ 5.5 mmol/l at least once and PPG was ≥ 7.8 mmol/l, or FPG was < 5.5 mmol/l but PPG was ≥ 7.8 mmol/l at least twice; if FPG was > 7.0 mmol/l and/or PPG > 10.0 mmol/l always started on insulin | M: FBG 5.9 ± 0.7 mmol/l; 2-hour BG 8.3 ± 1.8 mmol/l; HbA _{1c} 5.7 ± 0.4% I: FBG 6.3 ± 0.8 mmol/l; 2-hour BG 9.5 ± 2.2 mmol/l; HbA _{1c} 5.7 ± 0.4% p < 0.005 for FPG and 2-hour BG |

Values are mean ± SD unless indicated otherwise.

Appendix 6

Quality of included RCTs

| Study | Method of randomisation | Allocation concealment | Blinding | Intention to treat data analysis | Percentage who completed trial | Power calculation | Similarity of groups at baseline | Comments | Overall quality score (of 7) |
|---------------------------------|---|------------------------|--------------|----------------------------------|---|----------------------|--|---|------------------------------|
| Insulin vs glibenclamide | | | | | | | | | |
| Anjalakshi 2007 ⁶⁶ | N/R | Unclear | Probably not | N/R | 23 of 26 completed the trial | N/R | Yes, for parameters reported | | 2 |
| Bertini 2005 ⁶⁷ | Opaque envelopes | Unclear | No | No | 70/71 | N/R | Yes, for parameters reported | | 3 |
| Langer 2000 ⁶⁸ | Adequate | Yes | No | Yes | Unclear – all? | N/R | Yes, for parameters reported | | 4.5 |
| Ogunyemi 2007 ⁶⁹ | Computer-generated list; treatment assignment by sequentially numbered opaque envelopes | Yes | No | Yes | Glibenclamide: complete delivery records for 43/48 (89.6%) insulin: complete delivery records for 45/49 (91.8%) | N/R | No: no significant differences were noted between groups in maternal age, parity, BMI, history of previous gestational diabetes, previous neonatal macrosomia; results of 1-hour glucose challenge test, HbA _{1c} and fasting, 1-hour, and 2-hour results of 3-hour glucose tolerance test significantly higher at baseline in insulin group; 2-hour clinic PPG level (baseline?) significantly higher in glibenclamide group than insulin group; gestational age at enrolment was 4 weeks later in the glibenclamide group | Not a full report (published as a letter); data presentation not entirely clear, it looks like values referring to maternal glycaemic control are just pre-enrolment values | 3.5 |
| Insulin vs metformin | | | | | | | | | |
| Hague 2003 ⁸⁵ | N/R | N/R | Probably not | N/R | 100%? | No, pilot study only | Yes, for parameters reported | Not a full report (published as a letter) | 1 |

| Study | Method of randomisation | Allocation concealment | Blinding | Intention to treat data analysis | Percentage who completed trial | Power calculation | Similarity of groups at baseline | Comments | Overall quality score (of 7) |
|--------------------------------|--|------------------------|----------|---|---|---|--|----------|------------------------------|
| Moore 2007 ⁸⁶ | Computer-generated list, sequentially numbered opaque, sealed envelopes; next envelope selected by research nurse not involved with patient care | Yes | No | Not reported, but apparently no losses to follow-up | 100%? | Yes, but study only included half the patients necessary according to power calculation | Patients in the metformin group were significantly heavier; other baseline characteristics were not significantly different [although difference in ethnicity almost reached significance ($p = 0.077$)] | | 2.5 |
| Rowan 2008 ⁸⁸ (MIG) | N/R; block size of four, stratified according to site and gestational age, computerised | N/R | No | Yes | 97% in metformin group, 98% in insulin group, no significant difference | Yes | Yes, for most parameters reported; 23.1% of women in the metformin group vs 16.8% of those in the insulin group had had at least three pregnancy terminations or miscarriages ($p = 0.03$) | | 4.5 |

Values are mean \pm SD unless indicated otherwise.

Appendix 7

Quality of included cohort studies

| Study | Sufficient description of groups and distribution of prognostic factors? | Groups assembled at a similar point in disease progression? | Intervention reliably ascertained? | Groups comparable on all important confounding factors? | Adequate adjustment for the effects of these confounding variables? |
|---------------------------------|--|---|------------------------------------|--|---|
| Insulin vs glibenclamide | | | | | |
| Coetzee 1986 ⁷⁰ | No | Yes | Yes | N/R | N/R |
| Duncan 2005 ⁷¹ | No | N/R | Yes | As far as reported | N/R |
| Fines 2003 ⁷² | No | N/R | Yes | Yes, as far as reported | N/R |
| Gilson 2002 ⁷³ | No | N/R | Yes | Unclear | N/R |
| Goodman 2008 ⁷⁴ | No | N/R | Yes | As far as reported | N/R |
| Holt 2008 ⁵² | Yes | Yes | Yes | No, women choosing glibenclamide had a significantly higher baseline FBG, 2-hour PPG and HbA _{1c} than those choosing insulin; significantly more Asian women chose glibenclamide in preference to insulin; BMI in insulin group was significantly higher than in glibenclamide group | Yes |
| Jacobson 2005 ⁷⁵ | Yes | Yes | Yes | For most parameters; significantly higher BMI in insulin group; more women in the insulin group were white and fewer were Asian; some BG values significantly higher in insulin group | Yes |
| Langer 2006 ⁷⁶ | No | N/R | Yes | N/R | Yes |
| Patterson 2008 ⁷⁷ | No | Yes | Yes | Partially, as far as reported; women treated with insulin had a greater BMI (34.8 ± 8.3 kg/m ² vs 30.5 ± 6.1 kg/m ² , $p=0.006$) and required therapy earlier (27.1 ± 8.2 weeks vs 32.0 weeks, $p=0.002$) | N/R |
| Ramos 2007 ⁶¹ | Yes | Yes | Yes | For most parameters; significantly older women in the glibenclamide group; significantly higher BMI in the insulin group | Yes |
| Yogev 2004 ⁷⁸ | Yes | Yes | Yes | Yes, as far as reported | N/R |
| Glibenclamide failure | | | | | |
| Chmait 2004 ⁷⁹ | Yes | N/A | Yes | N/A (confounders = parameters investigated) | Yes |
| Conway 2004 ⁸⁰ | Yes, but a bit limited | Yes | Yes | N/A (confounders = parameters investigated) | Yes |
| Kahn 2006 ⁶³ | Yes | Yes | Yes | N/A (confounders = parameters investigated); pregnancy outcomes not reported for groups separately | Yes |

| Dose-response relationship between intervention and outcome? | Blind outcome assessment? | Follow-up long enough to occur? | Proportion of the cohort followed-up? | Dropout rates and reasons for drop-out similar across comparison groups? | Comments | Overall (of 10) |
|---|----------------------------------|--|--|---|--|------------------------|
| Yes | N/R | Yes | N/R | N/R | | 4 |
| N/R | N/R | Yes | N/A (retrospective) | N/A | Abstract only | 3 |
| N/R | N/R | Yes | N/A (retrospective) | N/A | Abstract only | 3 |
| N/R | N/R | Yes | All? | N/R | Abstract only | 3 |
| N/R | N/R | Yes | N/A (retrospective) | N/A | Abstract only | 3 |
| Yes | N/R | Yes | All? | N/R | | 7 |
| Yes | N/R | Yes | N/A (retrospective) | N/A | | 7 |
| Yes | N/R | Yes | N/R | N/R | Abstract only | 4 |
| N/R | N/R | Yes | N/A (retrospective) | N/A | Abstract only | 3.5 |
| Yes | No | Yes | N/A (retrospective) | N/A | Some overlap (30 insulin, 16 glibenclamide) with Jacobson 2005 ⁷⁵ | 6 |
| N/R | N/R | Yes | All? | N/R | | 5 |
| Yes | N/R | Yes | All? | N/R | | 7 |
| Yes | N/R | Yes | N/A (retrospective) | N/A | | 6 |
| N/R | N/R | Yes | N/A (retrospective) | N/A | | 5 |

| Study | Sufficient description of groups and distribution of prognostic factors? | Groups assembled at a similar point in disease progression? | Intervention reliably ascertained? | Groups comparable on all important confounding factors? | Adequate adjustment for the effects of these confounding variables? |
|--|---|--|---|---|--|
| Langer 2006 ⁸¹ | No | N/R | Yes | N/A (confounders = parameters investigated) | Yes |
| Parrish 2008 ⁸² | No | N/R | Yes | N/A (confounders = parameters investigated) | Yes |
| Rochon 2006 ⁸³ | Yes | Yes | Yes | N/A (confounders = parameters investigated) | Yes |
| Velazquez 2003 ⁸⁴ | No | N/R | Yes | N/R | N/R |
| <i>Insulin vs metformin</i> | | | | | |
| <i>Observational</i> | | | | | |
| Balani 2008 ⁸⁹ | No | N/R | Yes | N/R; groups matched for BMI and ethnicity | N/R |
| Tertti 2008 ⁵⁶ | Yes | Yes | Yes | For most parameters; metformin group had significantly lower OGTT values than insulin group; significantly more primiparous women in insulin group than metformin group | Yes |
| Values are mean ± SD unless indicated otherwise. | | | | | |

| Dose-response relationship between intervention and outcome? | Blind outcome assessment? | Follow-up long enough to occur? | Proportion of the cohort followed-up? | Dropout rates and reasons for drop-out similar across comparison groups? | Comments | Overall (of 10) |
|---|----------------------------------|--|--|---|-----------------|------------------------|
| Yes | N/R | Yes | N/R | N/R | Abstract only | 4 |
| N/R | N/R | Yes | N/A (retrospective) | N/R | Abstract only | 3 |
| N/R | N/R | Yes | N/A (retrospective) | N/A | | 6 |
| N/R | N/R | Yes | All? | N/R | Abstract only | 2 |
| N/R | N/R | Yes | N/R | N/R | Abstract only | 2.5 |
| Yes | N/R | Yes | N/A (retrospective) | N/A | | 7 |

Appendix 8

Summary of results of primary studies

| Outcome | Number of studies | Significance | Magnitude of effect | Occurrence of outcome (across study types) |
|---------------------------------------|---|---------------------------|--|--|
| Maternal/obstetric outcomes | | | | |
| <i>Pre-eclampsia</i> | | | | |
| Glibenclamide vs insulin | Two observational | One of two significant | Jacobson 2005: ⁷⁵ 6% (95% CI 1 to 11) more pre-eclampsia with glibenclamide | Mean 8%, range 2–12% |
| | One RCT, one observational | No significant difference | | |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | One RCT, two observational | No significant difference | | Mean 7%, range 5.5–19% |
| <i>Pregnancy-induced hypertension</i> | | | | |
| Metformin vs insulin | One RCT, two observational (one abstract) | No significant difference | | Mean 3.1%, range 0–6.2% |
| <i>Induction of labour</i> | | | | |
| Glibenclamide vs insulin | Two observational | No significant difference | | Mean 50.5%, range 49–52% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | Three RCTs, one observational | No significant difference | | Mean 54%, range 31–64% |
| <i>Caesarean delivery</i> | | | | |
| Glibenclamide vs insulin | Three observational abstracts | One of three significant | Duncan 2005: ⁷¹ 41% fewer caesarean deliveries for non-morbidly obese women with glibenclamide (but not for obese women) RR 0.53 (95% CI 0.36 to 0.77, $p=0.001$) | Mean 35%, range 10–56% |
| | Three RCTs, three observational, four observational | No significant difference | RCTs: RR 0.91 (95% CI 0.71 to 1.16) Observational: RR 1.04 (95% CI 0.84 to 1.28) Abstracts: Glibenclamide success vs failure: RR 0.78 (95% CI 0.55 to 1.09) | |
| Acarbose vs insulin | One RCT | No significant difference | RR 1.18 (95% CI 0.65 to 2.16) | Mean 48.5%, range 44–53% |
| Metformin vs insulin | Three RCTs, two observational | No significant difference | RCTs: RR 1.08 (95% CI 0.59 to 1.97) Observational: RR 1.40 (95% CI 0.70 to 2.81) | Mean 36%, range 21–63% |

| Outcome | Number of studies | Significance | Magnitude of effect | Occurrence of outcome (across study types) |
|-----------------------------------|--|---------------------------|---|---|
| <i>Maternal weight gain</i> | | | | |
| Glibenclamide vs insulin | Two observational | One of two significant | Jacobson 2005: ⁷⁵ 1.15 kg more weight gain with glibenclamide, $p=0.03$ | Mean 10.4 kg, range 9–12.7 kg |
| | Two RCTs, one observational glibenclamide success vs failure | No significant difference | | |
| Acarbose vs insulin | One RCT | No significant difference | | Mean 11.1 kg, range 10.6–11.5 kg |
| Metformin vs insulin | One RCT | Significant | 1.6 kg more weight gain with insulin from enrolment to 36/37 weeks of gestation, $p<0.001$ | Metformin: 0.4 ± 2.9 kg; insulin: 2.0 ± 3.3 kg |
| | Two observational | One of two significant | Balani 2008: ⁸⁹ 1.1 kg more weight gain with insulin (time interval uncertain) | Tertti 2008: ⁵⁶ 9.7–10.2 kg; Balani 2008: ⁸⁹ 0.3–1.4 kg |
| Maternal glycaemic control | | | | |
| <i>Glibenclamide vs insulin</i> | | | | |
| FBG (mmol/l) | One RCT | No significant difference | | Mean 5.4 mmol/l, range 4.88–6.32 mmol/l |
| | One observational | Significant | Jacobson 2005: ⁷⁵ FBG 0.41 mmol/l (95% CI –2.00 to –0.88, $p<0.05$) lower in glibenclamide success group | |
| | One observational glibenclamide success vs failure | Significant | Chmait 2004: ⁷⁹ FBG 1.44 mmol/l (95% CI –0.58 to –0.24, $p<0.05$) lower in glibenclamide group | |
| 2-hour PPG (mmol/l) | One RCT, one observational | No significant difference | | Mean 5.89 mmol/l, range 5.2–6.6 mmol/l |
| Mean BG (mmol/l) | One RCT, one observational | No significant difference | | Mean 5.8 mmol/l, range 5.78–5.83 mmol/l |
| HbA _{1c} (%) | Two RCTs | No significant difference | | Mean 5.4%, range 5.3–5.5% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | | | | |
| FBG (mmol/l) | Two RCTs | No significant difference | | Range 5.09–5.37 mmol/l |
| 2-hour PPG (mmol/l) | Two RCTs | One of two significant | Rowan 2008: ⁸⁸ 2-hour PPG –0.20 mmol/l lower in metformin group 1 week after randomisation and overall ($p<0.01$), but not during last 2 weeks before delivery | Range 5.9–6.69 mmol/l |
| HbA _{1c} (%) | One RCT | No significant difference | | Range 5.6–5.7% |

| Outcome | Number of studies | Significance | Magnitude of effect | Occurrence of outcome (across study types) |
|--------------------------------------|--|---|--|--|
| <i>Maternal hypoglycaemia</i> | | | | |
| Glibenclamide vs insulin | Three RCTs | One of three significant | Langer 2000: ⁶⁸ 18% less hypoglycaemia with glibenclamide than insulin ($p=0.03$) | Range 0.08–63% |
| | Two observational | Two of two significant but opposite direction | Jacobson 2005: ⁷⁵ 0.12% more hypoglycaemia with glibenclamide, $p<0.001$ Yogev 2004: ⁷⁸ 35% fewer women with hypoglycaemia with glibenclamide, $p=0.04$ | |
| Acarbose vs insulin | One RCT | No significant hypoglycaemia | | |
| Metformin vs insulin | One RCT | No hypoglycaemia | | |
| <i>Post-partum glucose tolerance</i> | | | | |
| Glibenclamide vs insulin | Not reported | | | |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | One RCT, one observational (abstract) | No significant difference | | - |
| Acceptability of treatment | See <i>Table 14</i> | | | |
| Maternal anxiety | Not reported | | | |
| Maternal depression | Not reported | | | |
| Maternal health status | Not reported | | | |
| Child/neonatal outcomes | | | | |
| <i>Neonatal hypoglycaemia</i> | | | | |
| Glibenclamide vs insulin | Three RCTs | One of three significant | Bertini 2005: ⁶⁷ 29% fewer neonates with hypoglycaemia with insulin, $p<0.05$ Overall RR 2.07 (95% CI 1.04 to 4.11, $p=0.04$) | Mean 22% glibenclamide, 15% insulin, range 0–34% |
| | Five observational (one abstract) | One of five significant | Ramos 2007: ⁶¹ 20% fewer neonates with hypoglycaemia with insulin, $p<0.05$ Overall RR 1.40 (95% CI 0.97 to 2.01, $p=0.07$) (full publications) | |
| | Three observational glibenclamide success vs failure | No significant difference | RR 0.74 (95% CI 0.31 to 1.78) | |
| Acarbose vs insulin | One RCT | No significant difference | | |

| Outcome | Number of studies | Significance | Magnitude of effect | Occurrence of outcome (across study types) |
|----------------------------|---|---------------------------|---|---|
| Metformin vs insulin | Two RCTs | No significant difference | RR 0.80 (95% CI 0.58 to 1.10) | Mean 15% metformin, 21% insulin, range 0–58% |
| | Two observational | One of two significant | Tertti 2008: ⁵⁶ 32% fewer neonates with hypoglycaemia with metformin, $p < 0.05$ Overall RR 0.60 (95% CI 0.38 to 0.95, $p = 0.03$) | |
| <i>Hyperbilirubinaemia</i> | | | | |
| Glibenclamide vs insulin | One RCT, two observational, one observational glibenclamide success vs failure | No significant difference | | Mean 15%, range 4–25% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | Two RCTs | No significant difference | | |
| | Two observational | One of two significant | Balani 2008 ⁸⁹ (abstract): 33.5% more neonates with hyperbilirubinaemia in the insulin group ($p < 0.05$) | Mean 27%, range 9–42.5% |
| <i>Phototherapy</i> | | | | |
| Glibenclamide vs insulin | Four observational | Two of four significant | Holt 2008 ⁵² /Jacobson 2005: ⁷⁵ 16%/5% fewer neonates in need of phototherapy with insulin than glibenclamide, $p < 0.05$ | Mean 11% glibenclamide, 7% insulin, range 4–33% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | Two RCTs, two observational | No significant difference | RCTs: RR 1.00 (95% CI 0.59 to 1.69) Observational: RR 0.89 (95% CI 0.56 to 1.42) | Mean 12%, range 0–33% |
| <i>Birthweight</i> | | | | |
| Glibenclamide vs insulin | Four RCTs, three observational, three observational glibenclamide success vs failure, two abstracts | No significant difference | RCTs: WMD 89.63 g (95% CI –1.48 to 180.75) Observational: WMD –45.49 g (95% CI –218.36 to 127.37) Glibenclamide success vs failure: WMD –22.05 g (95% CI –205.64 to 161.54) Abstracts: WMD –27.6 g (95% CI –115.49 to 60.29) | Range 2600–3661 g |
| Acarbose vs insulin | One RCT | No significant difference | WMD 91.4 g (95% CI –145.32 to 328.12) | Range 3151–3243 g |

| Outcome | Number of studies | Significance | Magnitude of effect | Occurrence of outcome (across study types) |
|----------------------------|---|---------------------------|---|--|
| Metformin vs insulin | Three RCTs, two observational | No significant difference | RCTs: WMD -34.28 g (95% CI -112.80 to 44.24) Observational: WMD 2.00 g (95% CI -254.34 to 258.34) | Range 3413–3761 g |
| <i>Macrosomia</i> | | | | |
| Glibenclamide vs insulin | Two RCTs, three observational, three observational glibenclamide success vs failure | No significant difference | RCTs: RR 2.39 (95% CI 0.50 to 11.35) Observational: RR 1.06 (95% CI 0.81 to 1.39) Glibenclamide success vs failure: RR 1.39 (95% CI 0.57 to 3.38) | Mean 15%, range 0–27% |
| | Four abstracts | One of four significant | Goodman 2008: ⁷⁴ 8% more macrosomia in insulin group, $p < 0.05$ Overall RR 0.37 (95% CI 0.16 to 0.84, $p = 0.02$) | |
| Acarbose vs insulin | One RCT | No macrosomia | | |
| Metformin vs insulin | Two RCTs, two observational | No significant difference | | Mean 16%, range 9–22% |
| <i>LGA</i> | | | | |
| Glibenclamide vs insulin | Two RCTs, three observational, two abstracts | No significant difference | RCTs: RR 1.95 (95% CI 0.29 to 13.09) Observational: RR 1.10 (95% CI 0.84 to 1.45) Abstracts: RR 0.91 (95% CI 0.51 to 1.62) | Mean 20%, range 4–64% |
| Acarbose vs insulin | One RCT | No significant difference | RR 2.84 (95% CI 0.28 to 29.14) | Mean 7.5%, range 4–11% |
| Metformin vs insulin | One RCT, one observational | No significant difference | | Mean 19%, range 15–19% |
| <i>SGA</i> | | | | |
| Glibenclamide vs insulin | One RCT, three observational | No significant difference | RCT: RR 0.22 (95% CI 0.01 to 4.45) Observational: RR 0.78 (95% CI 0.42 to 1.45) | Mean 6%, range 0–13% |
| Acarbose vs insulin | One RCT | No significant difference | RR 0.28 (95% CI 0.01 to 5.52) | Mean 3.5%, range 0–7% |
| Metformin vs insulin | One RCT, two observational | No significant difference | RCT: RR 0.74 (95% CI 0.45 to 1.19) Observational: RR 1.39 (95% CI 0.56 to 3.50) | Mean 9%, range 2–19% |
| <i>Perinatal mortality</i> | | | | |
| Glibenclamide vs insulin | Two RCTs, four observational, two observational glibenclamide success vs failure | No significant difference | | Mean 0%, range 0–2% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | Two RCTs, two observational | No significant difference | | Mean 0%, range 0–1% |

| Outcome | Number of studies | Significance | Magnitude of effect | Occurrence of outcome (across study types) |
|-----------------------------|---|---------------------------|--|--|
| <i>NICU admission</i> | | | | |
| Glibenclamide vs insulin | One RCT, three observational, two observational glibenclamide success vs failure, three abstracts | No significant difference | RCTs: RR 0.87 (95% CI 0.41 to 1.83) Observational: RR 0.75 (95% CI 0.53 to 1.05) Glibenclamide success vs failure: RR 2.22 (95% CI 0.64 to 7.73) | Mean 16%, range 6–33% |
| Acarbose vs insulin | One RCT | No NICU admissions | | |
| Metformin vs insulin | Two RCTs, two observational (one abstract) | One of four significant | Balani 2008: ⁸⁹ 14% fewer NICU admissions with metformin than with insulin, $p < 0.05$ | Mean 18% metformin, 24% insulin, range 5–62% |
| <i>Birth trauma</i> | | | | |
| Glibenclamide vs insulin | One RCT, two observational | No significant difference | | Mean 2%, range 0–4.5% |
| Acarbose vs insulin | One RCT | No birth trauma | | |
| Metformin vs insulin | One RCT, one observational | No significant difference | | Mean 4%, range 2–4.6% |
| <i>Shoulder dystocia</i> | | | | |
| Glibenclamide vs insulin | Three observational glibenclamide success versus failure, one abstract | No significant difference | | Mean 4.5%, range 0–9% |
| Acarbose vs insulin | One RCT | No birth trauma | | |
| Metformin vs insulin | Two RCTs, one abstract | No significant difference | | Mean 2%, range 0–3% |
| <i>Malformations</i> | | | | |
| Glibenclamide vs insulin | Two RCTs three observational, one observational glibenclamide success vs failure | No significant difference | | Mean 3%, range 0–10% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | One RCT, two observational | No significant difference | | Mean 4%, range 0–10% |
| <i>Respiratory distress</i> | | | | |
| Glibenclamide vs insulin | One RCT, three observational | No significant difference | | Mean 5%, range 2–9% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | Two RCTs, one observational | No significant difference | | Mean 4%, range 0–12.5% |
| <i>Apgar scores</i> | | | | |
| Glibenclamide vs insulin | One RCT, one observational, one observational glibenclamide success vs failure, three abstracts | No significant difference | | 1-minute Apgar range 7.3–8.2, 5-minute Apgar range 8.7–9.4 |
| Acarbose vs insulin | One RCT | No significant difference | | 1-minute Apgar range 8.1–8.4, 5-minute Apgar range 9.3–9.4 |

| Outcome | Number of studies | Significance | Magnitude of effect | Occurrence of outcome (across study types) |
|------------------------------------|--|---|--|--|
| Metformin vs insulin | One RCT, one observational | No significant difference | | 5-minute Apgar range 8.6–9 |
| <i>Preterm delivery</i> | | | | |
| Glibenclamide vs insulin | Two observational, two observational glibenclamide success vs failure, two abstracts | No significant difference | | Mean 13%, range 5–23% |
| Acarbose vs insulin | Not reported | | | |
| Metformin vs insulin | One RCT, one observational, one abstract | Two of three significant (opposite direction) | RCT Rowan 2008: ⁸⁸ 4.5% more preterm delivery with metformin ($p=0.04$) Abstract Balani 2008: ⁸⁹ 11% more pre-term deliveries with insulin ($p<0.01$) | Mean metformin 9%, insulin 8%, range 0–12% |
| <i>Gestational age at delivery</i> | | | | |
| Glibenclamide vs insulin | Three RCTs, three observational, two observational glibenclamide success vs failure, two abstracts | No significant difference | RCTs: WMD –0.11 weeks (95% CI –0.55 to 0.34) Observational: WMD –0.16 weeks (95% CI –0.44 to 0.13) Glibenclamide success vs failure: WMD 0.2 weeks (95% CI –0.30 to 0.71) | Range 37.6–39 weeks |
| Acarbose vs insulin | One RCT | No significant difference | | Range 38.2–38.5 weeks |
| Metformin vs insulin | Three RCTs, one observational | No significant difference | | Range 37.8–38.5 weeks |

Values are mean \pm SD unless indicated otherwise.

Appendix 9

Additional results – primary studies

| Study | Maternal | Neonatal |
|--------------------------------------|---|---|
| Glibenclamide vs insulin | | |
| <i>RCT</i> | | |
| Anjalakshi 2007 ⁶⁶ | None | No significant difference in cord blood insulin at birth No significant difference in neonatal BG |
| Bertini 2005 ⁶⁷ | None | One neonate from glibenclamide group required special care for 2 days in an intermediate unit No significant difference in neonatal BG |
| Langer 2000 ⁶⁸ | None | Ponderal index > 2.85: glibenclamide: 9%, insulin: 12%, $p=0.33$ No significant difference in cord serum insulin No significant difference in intravenous glucose therapy No significant difference in polycythaemia No significant difference in hypocalcaemia No significant difference in outcomes when stratifying women according to their mean glucose concentration measured at home (at least 5.9 mmol/l or no more than 5.8 mmol/l) No significant difference when stratifying women according to whether they entered study before or after 20 weeks' gestation |
| <i>Observational</i> | | |
| Fines 2003 ⁷² | None | Reports that there was no significant difference at study end between glibenclamide and insulin for gestational age at delivery, incidence of preterm delivery, Apgar scores at 1 and 5 minutes, NICU admission and ponderal index, but no data shown |
| Gilson 2002 ⁷³ | None | None |
| Holt 2008 ⁵² | None | None |
| Jacobson 2005 ⁷⁵ | None | No significant difference in polycythaemia No significant difference in hypocalcaemia |
| Patterson 2008 ⁷⁷ | No significant difference in post-partum haemorrhage, third and fourth degree perineal lacerations and intrapartum infections | Fetal cord gas pH: G: 7.26 ± 0.06 ; I: 7.21 ± 0.09 , $p=0.008$ Fetal cord gas P_{CO_2} : G: 55.3 ± 8.8 ; I: 61.2 ± 12.9 , $p=0.03$ |
| Ramos 2007 ⁶¹ | None | No significant difference in polycythaemia No significant difference in hypocalcaemia |
| Metformin vs insulin | | |
| <i>RCT</i> | | |
| Hague 2003 ⁸⁵ (MiG pilot) | None | None |
| Moore 2007 ⁸⁶ | One post-partum haemorrhage in a woman with shoulder dystocia in the metformin group | None |

| Study | Maternal | Neonatal |
|--|---|--|
| Rowan 2007/8 ^{87,88} (MiG) | Some maternal PPG values tended to be higher in the insulin group than in the metformin group ($p < 0.01$ for general values and 1 week after randomisation) No significant difference in OGTT 6–8 weeks' post partum | No significant difference in umbilical cord or scalp blood pH No difference in umbilical cord insulin concentration |
| <i>Observational</i> Tertti 2008 ⁵⁶ | | No significant difference in umbilical artery pH or base excess |
| Values are mean \pm SD unless indicated otherwise. | | |

Appendix 10

Criteria and characteristics regarding oral medication failure

| Study | Criteria for 'oral failure' | Number/proportion of oral failures | Number/proportion of inadequate control with insulin | Characteristics of 'failures' vs 'non-failures' |
|---------------------------------|--|--|--|---|
| Glibenclamide vs insulin | | | | |
| <i>RCT</i> | | | | |
| Anjalakshi 2007 ⁶⁶ | None | None | Not reported | N/A |
| Bertini 2005 ⁶⁷ | Maximum dosage reached without achieving glucose control (presumably defined as above for study entry?) | G: 5/24 (20.8%) A: 8/19 (42.1%) | Not reported | Not reported |
| Langer 2000 ⁶⁸ | If glucose values for a women on maximum dose of glibenclamide did not meet glucose goals for 2 weeks, switched to insulin | 8/201 (4%) 36/201 (18%) had home BG values not within desired range | 24/203 (12%) had home BG values not within desired range | Not reported |
| Moore 2005 ⁹⁵ | Inadequate control with maximum dose | 3/24 (12.5%) | N/A | Not reported |
| Ogunyemi 2007 ⁶⁹ | Not reported | 3/48 (6.3%) | Not reported | Not reported |
| <i>Observational</i> | | | | |
| Coetzee 1986 ⁷⁰ | Switched to insulin if combination of glibenclamide and metformin failed to control BG adequately | 39/165 (24%) | Not reported | Not reported |
| Duncan 2005 ⁷¹ | Not reported (retrospective study) | N/A | N/A | N/A |
| Fines 2003 ⁷² | Not reported (retrospective study) | N/A | N/A | N/A |
| Gilson 2002 ⁷³ | Unclear | 2/11 (18%) | 3/11 (27%) did not have satisfactory glycaemic control | Not reported |
| Goodman 2008 ⁷⁴ | Not reported (retrospective study) | N/A | N/A | N/A |

| Study | Criteria for 'oral failure' | Number/proportion of oral failures | Number/proportion of inadequate control with insulin | Characteristics of 'failures' vs 'non-failures' |
|------------------------------|--|--|---|--|
| Holt 2008 ⁵² | Women who were unable to achieve adequate control (according to BG goals) on glibenclamide (maximum dose) were switched to insulin | 10/44 (23%) 25/77 (32%) in Nasruddin 2009 ⁹² | Not reported; women switching to insulin achieved adequate control (by self-monitoring of BG) | Significantly higher pre-pregnancy BMI ($33.2 \pm 5.4 \text{ kg/m}^2$ vs $28.8 \pm 5.8 \text{ kg/m}^2$) in the 'failure' group; no difference in age, baseline glycaemia or third trimester ultrasound biometry; no apparent differences in birth outcomes |
| Jacobson 2005 ⁷⁵ | If glycaemic goals were not met on a maximum daily dose of 20 mg, patients were switched to insulin; glibenclamide failure defined as beginning insulin therapy after starting glibenclamide | 28/236 (12%) plus 11 (5%) who never switched to insulin Mean fasting and/or post-prandial values within goal for 86% (of 122) | Not reported Mean fasting and/or post-prandial values within goal for 63% (of 137), $p < 0.001$ vs glibenclamide | No comparative data but the following statistics: women who switched to insulin had mean BMI 31.6 kg/m^2 , FBG 104.8 mg/dl 5.82 mmol/l ; neonates: mean birthweight 3858 g , no birth injuries; women who stopped glibenclamide and did not switch to insulin: BMI 30.8 kg/m^2 , FBG 5.26 mmol/l ; neonates: mean birthweight 3893 g , no birth injuries |
| Langer 2006 ⁷⁶ | Not reported | Not reported | Not reported | Not reported |
| Patterson 2008 ⁷⁷ | N/A (retrospective) | N/A (retrospective) | N/A (retrospective) | N/A (retrospective) |
| Ramos 2007 ⁶¹ | Beginning insulin therapy after starting glibenclamide for any reason | 7/44 (16%) | Not reported | No comparative data but the following statistics: women who switched to insulin had mean BMI 28.4 kg/m^2 , FBG 6.3 mmol/l ; neonates: mean birthweight 3899 g , one birth injury, two neonatal hypoglycaemia |
| Yogev 2004 ⁷⁸ | Not reported | Not reported | Not reported | Not reported |

| Study | Criteria for 'oral failure' | Number/proportion of oral failures | Number/proportion of inadequate control with insulin | Characteristics of 'failures' vs 'non-failures' |
|---|--|------------------------------------|--|--|
| <i>Glibenclamide failure (predictors)</i> | | | | |
| Chmait 2004 ⁷⁹ | More than 20% of capillary BG levels above the desired range for a week while on the maximum dose of glibenclamide | 13/69 (18.8%) | Not reported | <p>Women with glibenclamide success significantly older, significantly more weeks of gestation at diagnosis of GDM and dietary failure, significantly less previous macrosomia (22% vs 54%)</p> <p>No significant difference in ethnicity, weight, nulliparity, family history of diabetes, previous GDM, duration of glibenclamide use, results of glucose tolerance tests</p> <p>During treatment, FBG significantly lower in success than failure group (4.9 ± 0.6 mmol/l vs 6.3 ± 0.9 mmol/l, $p < 0.001$)</p> <p>During treatment, 1-hour PPG significantly lower in success than failure group (6.9 ± 0.7 mmol/l vs 8.0 ± 1.1 mmol/l, $p < 0.001$)</p> <p>No significant difference in gestational age at delivery, route of delivery, birthweight, Apgar scores, prematurity, macrosomia, shoulder dystocia, fetal anomaly, admission to NICU, hyperbilirubinaemia</p> <p>Predictors for glibenclamide success: (1) dietary therapy failure after 30 weeks' gestation, and (2) dietary therapy failure at less than 30 weeks' gestation with mean FBG ≤ 6.1 mmol/l (110 mg/dl) and mean 1-hour PPG ≤ 7.8 mmol/l (140 mg/dl); sensitivity 98%, specificity 65%</p> |
| Conway 2004 ⁸⁰ | Failure to achieve adequate glycaemic control with glibenclamide resulted in conversion to insulin or delivery if the women were > 38 weeks' gestation | 12/75 (16%) | Not reported; 8/12 (67%) women switching to insulin also failed to achieve adequate control on insulin | <p>No significant difference between glibenclamide success and failure in maternal age, BMI, parity, prior history of GDM, first-degree relative with DM, macrosomia in prior pregnancy, gestational age at abnormal GCT or OGTT, GCT result</p> <p>Fasting, 1-hour, 2-hour and 3-hour values on OGTT all significantly lower in the glibenclamide success group ($p = 0.02$ to < 0.01)</p> <p>No significant difference in macrosomia, birthweight, or neonatal hypoglycaemia</p> |

| Study | Criteria for 'oral failure' | Number/proportion of oral failures | Number/proportion of inadequate control with insulin | Characteristics of 'failures' vs 'non-failures' |
|----------------------------|--|--|---|--|
| Kahn 2006 ¹⁴⁶ | Inability to maintain at least 80% of FBG and 1-hour PPG in the target range using maximum dose of glibenclamide for at least 1 week | 18/95 (19%) | Of 18 patients switched to insulin, 45% achieved adequate control | <p>Patients failing glibenclamide were significantly older and had a significantly greater gravidity and parity</p> <p>Patients failing glibenclamide were diagnosed with GDM and started treatment at significantly earlier gestational ages than glibenclamide success women</p> <p>No significant difference between glibenclamide failure and success in maternal BMI, cigarette smoking, history of GDM or weight gain during pregnancy</p> <p>FBG on 3-hour OGTT was significantly higher in women failing glibenclamide</p> <p>Of 18 patients switched to insulin, only 45% achieved adequate control</p> <p>Maternal and neonatal outcomes were only reported for the whole group, not for glibenclamide failure and success groups separately</p> |
| Langer 2006 ⁸¹ | Achieving BG target levels | With < 10 mg/dl dose, 60% achieved mean BG and 76% achieved 2-hour PPG; including patients on dose > 10 mg/dl, 85% achieved target glycaemic control | Not reported | <p>Of 40% of glibenclamide patients who failed to reach glycaemic control targets, 73% had a maximal dose of < 10 mg/dl and 27% failed when the dose was > 10 mg/dl</p> <p>Logistic regression of variables relating to glibenclamide success revealed that glibenclamide dose (> 10 mg/dl) ($p=0.00002$), GDM severity (defined by FPG levels) ($p=0.007$), ethnicity ($p=0.0001$) and maternal age ($p=0.0009$) were significant contributors; obesity, previous GDM, gestational age at diagnosis and parity did not contribute to failure rate</p> |
| Parrish 2008 ⁸² | Not reported | 14/58 (24.1%) | Not reported | <p>Significant predictors of failure were earlier gestational age at diagnosis and at initiation of treatment ($p<0.001$)</p> <p>Non-significant trends for personal history of gestational diabetes and first degree relative with diabetes</p> <p>The caesarean section rate was 38.6% in the success group and 64% in the failure group</p> <p>Neonatal/fetal outcomes were similar between the groups</p> |

| Study | Criteria for 'oral failure' | Number/proportion of oral failures | Number/proportion of inadequate control with insulin | Characteristics of 'failures' vs 'non-failures' |
|--------------------------------------|---|------------------------------------|--|---|
| Rochon 2006 ⁸³ | If glycaemic goals could not be achieved on maximum dose of glibenclamide or if glibenclamide was not tolerated for any reason, patient was considered to have failed glibenclamide and was switched to insulin | 21/101 (21%) | Not reported | No significant difference between glibenclamide failure and success in maternal age, ethnicity, multiparity, BMI, mean gestational age at diagnosis, fasting and 2-hour OGTT values, history of GDM, family history of DM Mean glucose values on GCT and proportion of values ≥ 200 mg/dl significantly higher in the failure than in the success groups 1-hour value on the OGTT significantly higher and 3-hour value significantly lower in the failure than in the success groups No significant difference between groups in mean gestational age at delivery, preterm delivery, caesarean delivery, mean birthweight, macrosomia, shoulder dystocia, 5-minute Apgar < 7, length of NICU stay Significantly more cases of NICU admission in success group than in failure group (mostly because of hypoglycaemia) |
| Velazquez 2003 ⁸⁴ | Inadequate control with maximum dose | 7/38 (18%) | Not reported | Not reported |
| Metformin vs insulin | | | | |
| <i>RCT</i> | | | | |
| Hague 2003 ⁸⁵ (MiG pilot) | Not reported | Not reported | Not reported | Not reported |
| Moore 2005 ⁹⁵ | Inadequate control with maximum dose (presumably) | 5/22 (23%) | N/A | Not reported |
| Moore 2007 ⁸⁶ | Patients taking maximum dose with two values exceeding goals for measurement period for 2 consecutive weeks were considered metformin failures and started on insulin | No metformin failures | Not reported | N/A |

| Study | Criteria for 'oral failure' | Number/proportion of oral failures | Number/proportion of inadequate control with insulin | Characteristics of 'failures' vs 'non-failures' |
|-------------------------------------|---|--|--|---|
| Rowan 2007/8 (MiG) ^{87,88} | If targets not achieved on metformin alone (maximum dose), insulin was added | 168/363 (46.3%) required supplemental insulin, 27 (7.4%) stopped metformin before delivery | Not reported | <p>Metformin alone vs supplemental insulin</p> <p>The supplemental insulin group had a significantly higher BMI than the metformin alone group ($p=0.01$)</p> <p>There were significantly fewer European/white and Chinese/south-east Asian women in the supplementary insulin group and significantly more Polynesians</p> <p>Significantly fewer women in the supplemental insulin group were nulliparous</p> <p>Significantly more women in the supplementary insulin group had had GDM previously, significantly more had three or more terminations or miscarriages and significantly more had a maternal family history of diabetes</p> <p>OGTT and enrolment FBG and HbA_{1c} were all significantly higher in the supplementary insulin group</p> <p>There was no significant difference between the metformin alone vs supplemental insulin in the primary composite outcome or in any of the individual outcomes of the composite (neonatal hypoglycaemia, respiratory distress, phototherapy, birth trauma, Apgar <7 at 5 minutes, prematurity <37 weeks)</p> |
| <i>Observational</i> | | | | |
| Balani 2008 ⁸⁹ | If targets not achieved on metformin alone (maximum dose), insulin was added (presumably) | 9/80 (11%) required additional insulin | Not reported | Not reported |
| Tertti 2008 ⁵⁶ | Unclear, just stated that in women treated with metformin, insulin was subsequently used as a supplementary treatment if required | 8/45 (18%) | Not reported | Not reported |

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We look forward to hearing from you.