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Oral anti-diabetic agents for women with pre-existing diabetes mellitus/impaired glucose tolerance or previous gestational diabetes mellitus

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Abstract

Background—While most guidelines recommend the use of insulin in women whose pregnancies are affected by pre-existing diabetes, oral agents have obvious benefits for patient acceptability and adherence. It is necessary, however, to assess the effects of these anti-diabetic agents on maternal and infant health outcomes. Additionally, women with previous gestational diabetes mellitus are increasingly found to be predisposed to impaired glucose tolerance and, despite the potential need for intervention for these women, there has been little evidence about the use of oral anti-diabetic agents by these women pre-conceptionally or during a subsequent pregnancy.

Objectives—To investigate the effect of oral anti-diabetic agents in women with pre-existing diabetes mellitus, impaired glucose tolerance or previous gestational diabetes planning a pregnancy or pregnant women with diabetes mellitus on maternal and infant health.

The use of oral antidiabetic agents for management of gestational diabetes in a current pregnancy is evaluated in a separate Cochrane review.

Search methods—We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2010).

Selection criteria—We included randomised and quasi-randomised trials.

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CONTRIBUTIONS OF AUTHORS

Joanna Tieu wrote the protocol and review with help from Philippa Middleton. Philippa Middleton, Suzette Coat and William Hague were involved in editing.

DECLARATIONS OF INTEREST

Suzette Coat and William Hague are involved in the conduct of the Metformin in the Prevention of Gestational Diabetes: The MPG Trial. This study aims to determine whether prophylactic treatment with Metformin from early in the second trimester of pregnancy will reduce the incidence and severity of gestational diabetes in women who previously had gestational diabetes.

Data collection and analysis—Two review authors independently assessed trial eligibility for inclusion.

Main results—We identified 13 trials published as 25 papers using the Cochrane Pregnancy and Childbirth group literature search, and an additional ongoing trial. We have not included any trials in the review. One trial is awaiting assessment and we have excluded twelve trials because they evaluated treatment of women with gestational diabetes or women with polycystic ovary syndrome, were not randomised controlled trials or data were not available.

Authors' conclusions—Little randomised evidence is available evaluating the use of oral anti-diabetic agents in women with diabetes mellitus, impaired glucose tolerance, previous gestational diabetes mellitus planning a pregnancy or pregnant women with pre-existing diabetes mellitus. Large trials comparing any combination of oral anti-diabetic agent, insulin and dietary and lifestyle advice in these women, reporting on maternal and infant health outcomes, glycaemic control, women's views on the intervention and long-term health outcomes for mother and child, are required to guide clinical practice.

Medical Subject Headings (MeSH)

Administration, Oral; Diabetes Mellitus [* drug therapy]; Diabetes, Gestational [drug therapy]; Glucose Intolerance [* drug therapy]; Hypoglycemic Agents [* administration & dosage]

MeSH check words

Female; Humans; Pregnancy

BACKGROUND

Pre-existing diabetes mellitus in pregnancy

Pre-existing, or pre-gestational diabetes includes pregnant women who have been previously diagnosed with type 1 or type 2 diabetes or, in rare cases, other forms of diabetes mellitus. While some parts of the world have a significantly greater prevalence of diabetes than others, globally it is estimated that the prevalence of diabetes for adults aged 20-79 years in 2010 was 6.6%; this is projected to reach 7.8% by 2030, with 7.9% of adults having impaired glucose tolerance in 2010 (projected to increase to 8.4% by 2030) a total of 900 million people in both groups combined by 2030 (IDF 2009). It is predicted that approximately one in three people with diabetes are undiagnosed (Cowie 2006). In pregnancy, the prevalence of pre-existing diabetes is reported as being up to 1.3% and is increasing (Bell 2008; Lawrence 2008). In particular, the rate of type 2 diabetes in pregnancy is rising faster than that of type 1 diabetes in pregnancy (Bell 2008; Lawrence 2008). These trends are further modified by maternal age and ethnicity, with a higher prevalence of pre-existing diabetes with increasing maternal age (Lawrence 2008).

In addition to the impact of diabetes on health, pre-existing diabetes in pregnancy is commonly associated with a number of adverse health outcomes for both the woman and child. In pregnant women, pre-existing diabetes has been associated with caesarean section, hypertension in pregnancy and preterm birth (Langer 2000; Ray 2001; Walkinshaw 2005).

Pregnancy in women with pre-existing diabetes may also exacerbate the effects of diabetes on renal function and retinopathy (Leguizamón 2007; Sheth 2002). Pre-existing diabetes in pregnancy is associated with an increased risk of fetal congenital anomaly and spontaneous abortion (Kitzmilller 1996). Fetal hyperinsulinaemia associated with pre-gestational diabetes affects infants by increasing the incidence of macrosomia (birthweight greater than 4000 g), large-for-gestational age (birthweight greater than 90th centile for age), shoulder dystocia, neonatal hypoglycaemia, preterm birth, hyperbilirubinaemia, hypocalcaemia and neonatal intensive care admission (Jensen 2004; Macintosh 2006; Ray 2001; Walkinshaw 2005; Weintrob 1996). Furthermore, long-term follow up of infants of diabetic mothers suggests that exposure to maternal diabetes in utero increases the risk of obesity and type 2 diabetes for these children in the future (Dabelea 2000).

Management of pre-existing diabetes mellitus before and during pregnancy

Adverse outcome in women with pre-existing diabetes and their infants is related to the level of glycaemic control achieved during pregnancy. Therefore, in pre-conception and antenatal care there is a strong focus on the management of maternal glucose concentrations.

Prior to conception, it is recommended that women with diabetes receive multidisciplinary care including an assessment of diabetes complications, advice on glycaemic control, diet, the importance of family planning, maternal diabetes complications and fetal risks (ADIPS 2005; Meltzer 2003; NICE 2008). Continuation of this care and additional monitoring of fetal growth are recommended for the duration of pregnancy (NICE 2008). Oral anti-diabetic agents are more commonly used by those with type 2 diabetes than those with type 1 diabetes, who will not achieve adequate glycaemic control on oral anti-diabetics alone. It is currently recommended that oral anti-diabetic agents be substituted with insulin therapy in women planning pregnancy and during pregnancy (ADIPS 2005; NICE 2008).

Oral anti-diabetic agents and use in pre-existing diabetes

Oral anti-diabetic agents, commonly referred to as oral hypoglycaemic agents or oral anti-hyperglycaemic agents, act in a variety of ways. While widely used in men and women suffering type 2 diabetes, their use in women planning a pregnancy or during pregnancy has been controversial, with conflicting reports on the safety of these agents in pregnancy. Because of concerns over the safety of oral agents, insulin is the preferred agent for glycaemic management in women with pre-existing diabetes in pregnancy (ADA 2004; ADIPS 2005; Kitzmilller 2008; Meltzer 2003). Current recommendations suggest that women planning or continuing pregnancy use insulin, although oral anti-diabetic agents may be considered on an individual basis since the harm from uncontrolled diabetes may outweigh any potential harm from oral antidiabetic agents.

While the lack of safety data in pregnancy of oral anti-diabetic agents has prevented them from being recommended for use during pregnancy, it is also argued that the use of oral anti-diabetic agents alone, including glyburide (glibenclamide) and metformin, may be inadequate to successfully manage the post-prandial glycaemic peaks associated with type 2 diabetes mellitus (Jovanovic 2007). However, oral anti-diabetic agents are convenient, preferable to insulin injections and do not require the intensive education associated with

insulin therapy. Where oral agents alone are not sufficient to achieve glycaemic control, they may also be used in combination to reduce the frequency or dose of insulin therapy. A retrospective study of diabetic women in South Africa who remained on oral anti-diabetic agents, transferred from oral agents to insulin and those who transferred from diet alone to insulin reported no difference in fetal anomaly rates (Ekpebegh 2007). This study did, however, report a significantly higher perinatal mortality rate in those continuing on oral anti-diabetic agents alone than those who were on insulin therapy. Meta-analyses and reviews of observational studies have been unable to provide definitive conclusions on the effects of oral anti-diabetic agents for the treatment of diabetes in pregnancy (Gutzin 2003; Ho 2007).

Common anti-diabetic agents used include sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides and peptide analogues. Biguanides, including metformin, reduce peripheral insulin resistance, inhibit gluconeogenesis and reduce plasma triglyceride concentrations (DeFronzo 1995; Stumvoll 1995; Yogeve 2004). Metformin does cross the placenta and therefore there have been concerns about its use in pregnancy (Hellmuth 2000; Kovo 2007; NICE 2008; Slocum 2002). The use of metformin for the treatment of gestational diabetes has been evaluated in a randomised controlled trial (Rowan 2008). This trial found that compared with insulin, metformin was not associated with increased perinatal complications, with a tendency to less severe neonatal hypoglycaemia, with less maternal weight gain and a greater acceptability of metformin treatment. In this study metformin treatment was commenced in the latter half of pregnancy, between 20 and 34 weeks' gestation. Although it has been suggested that metformin increases the odds of pregnancy and prevents pregnancy loss in women with polycystic ovary syndrome (PCOS), there is no definitive evidence on its safety in pregnancies, especially those complicated by pre-existing diabetes (Brock 2005; Ho 2007). Follow up at age 18 months of 126 infants born to 109 mothers with PCOS who conceived on and continued metformin during pregnancy reported similar size and motor-social development in the metformin exposed infants compared with infants of women not known to have PCOS (Glueck 2004).

Sulfonylureas act to enhance insulin secretion and peripheral tissue sensitivity to insulin while also reducing hepatic clearance of insulin (DeFronzo 1984; Homko 2006; Simonson 1984; Yogeve 2004); examples include glyburide (glibenclamide) and glimepiride. The main side effect of these agents is hypoglycaemia and while first generation sulfonylureas cross the placenta, it is unclear whether second generation agents, including glyburide (glibenclamide), do and what effect this has on the developing fetus (Jovanovic 2007; Kraemer 2006; Sivan 1995; Slocum 2002). A major concern is the ability of sulfonylureas to stimulate fetal hyperinsulinaemia (Coetzee 2007). However, a randomised controlled trial of treatment of women with gestational diabetes using glyburide (glibenclamide), a second generation sulfonylurea, or insulin, found that there were no differences in macrosomic or large-for-gestational-age infants between the two groups (Langer 2000).

Alpha-glucosidase inhibitors such as acarbose and miglitol reduce postprandial glucose levels by decreasing the breakdown and absorption of carbohydrates in the intestine (Slocum 2002; Yogeve 2004). There has been little evidence of the use of these agents in pregnancy

(Ho 2007). Alpha-glucosidase inhibitors are typically used in combination with other oral anti-diabetic agents or insulin (Yogev 2004).

Thiazolidinediones, including rosiglitazone and pioglitazone, result in increased insulin sensitivity and decreased lipid availability (Slocum 2002; Yogev 2004). There is little evidence on the use of thiazolidinediones in pregnancy (Ho 2007). However, placental transfer of thiazolidinediones has been reported (Chan 2005). Furthermore, caution has been placed on the use of rosiglitazone in type 2 diabetics due to an increased risk of adverse cardiovascular outcomes (Nissen 2007).

Meglitinides act by increasing pancreatic insulin secretion. There is little evidence of their use in pregnancy (Slocum 2002). Similarly, we could find no evidence on the use of peptide analogues such as incretin mimetics and dipeptidyl peptidase-4 inhibitors in pregnancy.

Previous gestational diabetes and management before and during pregnancy

Gestational diabetes mellitus (GDM) is 'carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy' (WHO 1999). GDM affects approximately 7% of all pregnancies and is associated with an increased risk of a number of adverse perinatal outcomes including macrosomia, shoulder dystocia, perineal trauma, pre-eclampsia (hypertension in pregnancy), and neonatal hypoglycaemia. Although gestational diabetes resolves in 90% of cases, women with a history of gestational diabetes represent a unique group of women who are at significant risk for developing recurrent GDM and for later development of type 2 diabetes mellitus (Kim 2002; Kim 2007). A history of GDM has also been associated with insulin resistance and impaired insulin secretion (Damm 1995; Seghieri 2007).

Despite the potential need for intervention for these women, there is little evidence on the use of oral agents pre-conceptionally or during pregnancy.

The most appropriate form of treatment for gestational diabetes in a current pregnancy is unclear. The Cochrane review 'Treatment of gestational diabetes' (Alwan 2009) compares treatment options for women with GDM, including the use of oral anti-diabetic agents such as metformin and glyburide (glibenclamide). It found that while women with GDM should be considered for treatment, it is unclear which treatment option should be offered.

Recently, the results of the Metformin in Gestational diabetes trial suggests that the use of metformin compared with insulin is not associated with increased perinatal complications (Rowan 2008). Although 46.30% of women in the metformin arm required supplemental insulin, women preferred metformin to insulin treatment. Follow up of these women and their children is ongoing.

Rationale for review

With the increasing prevalence of type 1, type 2 and gestational diabetes, there is an increasing need for evidence-based management of women with pre-existing diabetes or a history of gestational diabetes pre-conceptionally and during pregnancy. While most guidelines recommend the use of insulin in place of oral anti-diabetic agents, oral agents have obvious benefits for patient acceptability and adherence. Furthermore, there is little

evidence on the efficacy of these agents on maternal and infant health. It is therefore necessary to assess the benefits and harms of anti-diabetic agents in women with pre-existing diabetes planning pregnancy and during pregnancy. The use of oral antidiabetic agents for management of gestational diabetes in a current pregnancy is evaluated in the Cochrane review 'Treatment of gestational diabetes' (Alwan 2009).

OBJECTIVES

To investigate the effect of oral anti-diabetic agents in women with pre-existing diabetes mellitus, impaired glucose tolerance or previous gestational diabetes planning a pregnancy or pregnant women with diabetes mellitus on maternal and infant health.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised and quasi-randomised controlled trials.

Types of participants—Women with diabetes mellitus, impaired glucose tolerance or previous gestational diabetes mellitus planning a pregnancy or pregnant women with diabetes mellitus.

Types of interventions

1. Oral anti-diabetic versus no medication
2. Oral anti-diabetic versus another oral anti-diabetic
3. Oral anti-diabetic versus insulin
4. Oral anti-diabetic versus insulin + oral anti-diabetic
5. Oral anti-diabetic + insulin versus insulin
6. Different regimens of any of the above

Types of outcome measures

Primary outcomes

Maternal

1. Hypoglycaemic events
2. Use of insulin/additional method of glycaemic control (what type, duration, dosage)
3. Complications of diabetes (retinopathy, neuropathy, nephropathy, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease)

Infant

1. Live born, normally grown, healthy baby born at term
2. Macrosomia

3. Neonatal hypoglycaemia (requiring and/or not requiring treatment)

Secondary outcomes

Maternal

1. Spontaneous abortion/miscarriage
2. Therapeutic abortion
3. HbA_{1c}
4. Fasting/post-prandial glucose concentration
5. Diabetic ketoacidosis
6. Hyperglycaemic hyperosmolar state
7. Pre-eclampsia
8. Pregnancy hypertension
9. Blood pressure
10. Use of anti-hypertensive medication
11. Mode of birth (normal vaginal, operative vaginal, caesarean section)
12. Shoulder dystocia
13. Gestational diabetes
14. Induction of labour
15. Preterm birth
16. Placental abruption
17. Postpartum haemorrhage
18. Postpartum infection
19. Perineal trauma/tearing
20. Weight gain in pregnancy
21. Breastfeeding at discharge
22. Psychological impact of treatment
23. Maternal inconvenience (number of hospital visits, days in hospital, extra investigations, antenatal tests, acceptability of medication)

Long-term outcomes for mother

1. Postnatal HbA_{1c}
2. Postnatal complications of diabetes (retinopathy, neuropathy, nephropathy, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease)
3. Postnatal blood pressure

4. Postnatal body mass index (BMI)
5. Type 1 diabetes mellitus, type 2 diabetes mellitus or impaired glucose tolerance
6. Subsequent gestational diabetes

Infant

1. Perinatal mortality (stillbirth, neonatal or infant death)
2. Congenital malformation
3. Neonatal hyperbilirubinaemia (requiring and/or not requiring phototherapy)
4. Respiratory distress syndrome
5. Large-for-gestational age
6. Small-for-gestational age
7. Birthweight
8. Birthweight centile
9. Gestational age at delivery
10. Admission to neonatal nursery
11. Length of hospital stay
12. Birth injury/trauma (nerve palsy, fracture, intracranial haemorrhage)
13. One-minute Apgar less than seven
14. Five-minute Apgar less than seven
15. Polycythaemia
16. Hypocalcaemia
17. Hypercalcaemia
18. Ponderal index
19. Neonatal infection
20. Cord blood measures (anti-diabetic agent and insulin/c-peptide)
21. Neonatal anthropometry
22. Neonatal cardiomyopathy

Long-term outcomes for infant

1. Bayley scale of infant development (12 to 42 months)
2. Griffith mental development scale
3. Type 1 diabetes, type 2 diabetes or impaired glucose tolerance
4. Obesity

5. BMI
6. Anthropometry (skinfold thickness, fat mass)
7. Blood pressure
8. Dyslipidaemia
9. Gestational diabetes

Search methods for identification of studies

Electronic searches—We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (March 2010).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies—Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion or, if required, we consulted a third author.

Data extraction and management—We designed a form to extract data. We identified no eligible studies. For eligible studies, at least two review authors would have extracted the data using the agreed form. We would have resolved discrepancies through discussion or, if required, we would have consulted a third author. We would have entered data into Review Manager software (RevMan 2008) and checked for accuracy. When information regarding any of the above was unclear, we would have attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies—We planned for two review authors to independently assess risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We would have resolved any disagreement by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias): We planned to describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We planned to assess the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator),
- inadequate (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) or,
- unclear.

(2) Allocation concealment (checking for possible selection bias): We planned to describe for each included study the method used to conceal the allocation sequence and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We planned to assess the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes , alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias): We planned to describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We would consider that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We would assess blinding separately for different outcomes or classes of outcomes.

We planned to assess the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations): We planned to describe for each included study, and for

each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We planned to state whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake in future updates.

We planned to assess methods as:

- adequate;
- inadequate;
- unclear.

(5) Selective reporting bias: We planned to describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We planned to assess the methods as:

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias: We planned to describe for each included study any important concerns we have about other possible sources of bias.

We planned to assess whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias: We planned to make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2009). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings. We would have explored the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

Dichotomous data: For dichotomous data, we planned to present results as summary risk ratio with 95% confidence intervals.

Continuous data: For continuous data, we planned to use the mean difference if outcomes were measured in the same way between trials. We planned to use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials: We planned to include cluster-randomised trials in the analyses along with individually randomised trials. We planned to adjust their sample sizes using the methods described in Gates 2005 using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources had been used, we planned to report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identified both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We would also have acknowledged heterogeneity in the randomisation unit and performed a separate meta-analysis.

Crossover trials: We planned to exclude crossover trials from this review.

Dealing with missing data—For included studies, we planned to note levels of attrition. The impact of including studies with high levels of missing data in the overall assessment of treatment effect would have been explored by using sensitivity analysis.

For all outcomes, we planned to carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we planned to attempt to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial would be the number randomised minus any participants whose outcomes are known to be missing.

Where we were unable to extract data from publications of trials, we planned to contact author(s) or site, seeking clarification or data as required. We would acknowledge the efforts of these authors in the review.

Assessment of heterogeneity—We planned to assess statistical heterogeneity in each meta-analysis using the T^2 , I^2 and Chi^2 statistics. We would regard heterogeneity as substantial if I^2 is greater than 30% and either T^2 is greater than zero, or there is a low P-value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases—If there were 10 or more studies in the meta-analysis we would investigate reporting biases (such as publication bias) using funnel plots. We would assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we would use the test proposed by Egger 1997, and

for dichotomous outcomes we would use the test proposed by Harbord 2006. If we detect asymmetry in any of these tests or by a visual assessment, we would perform exploratory analyses to investigate it.

Data synthesis—We planned to carry out statistical analysis using the Review Manager software (RevMan 2008). We planned to use random-effects meta-analysis for combining data from trials.

Subgroup analysis and investigation of heterogeneity—We planned to carry out the following subgroup analyses:

1. type of diabetes (type I diabetes mellitus, type II diabetes mellitus, impaired glucose tolerance, previous gestational diabetes mellitus);
2. polycystic ovary syndrome (present or not);
3. glycaemic control (glycaemic targets achieved or not; e.g. pre-conception, 1st trimester, 2nd trimester, 3rd trimester).

We planned to use primary outcomes in subgroup analysis.

For fixed-effect meta-analyses we planned to conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. For random-effects meta-analyses, we planned to assess differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicate a statistically significant difference in treatment effect between the subgroups.

Sensitivity analysis—We planned to carry out sensitivity analysis on primary outcomes to explore the effect of trial quality assessed by allocation concealment and other risk of bias components, by omitting studies rated as inadequate for these components. If we had included cluster-randomised or quasi-randomised trials, we planned to perform sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search—A total of 26 trials were identified. The Cochrane Pregnancy and Childbirth group literature search identified 13 trials published as 25 papers to be considered for inclusion, and we identified one ongoing trial.

We included no trials in the review, and excluded 12 trials. One trial (Hutchinson 2008) is awaiting assessment and one trial is ongoing (Hague 2010). Hutchinson 2008 compares a combination of glyburide and metformin with insulin for glycaemic control in women with pre-existing type 2 diabetes mellitus or gestational diabetes mellitus not previously requiring insulin. We are awaiting full publication of this trial for inclusion in the review. Hague 2010

is a randomised controlled trial comparing, in women with a history of gestational diabetes, the use of extended release metformin with placebo on maternal and infant health outcomes.

Included studies—No trials identified by the literature search were eligible for inclusion.

Excluded studies—Of the studies excluded from the review, seven trials evaluated treatment of women with gestational diabetes mellitus in this pregnancy (Anjalakshi 2007; Bertini 2005; Golladay 2006; Hague 2003; Langer 2000; Moore 2005; Moore 2007; Rowan 2008), three trials evaluated treatment of women with polycystic ovary syndrome (Carlsen 2007; Vanky 2004; Vanky 2006) and one trial (Notelovitz 1971) presented combined data for women with type 2 diabetes mellitus and gestational diabetes mellitus. The study site was unable to retrieve the original data set to separate into these categories.

Studies evaluating management of gestational diabetes mellitus in the current pregnancy are considered in Alwan 2009. A separate Cochrane review (Tang 2010) evaluates the use of insulin sensitising agents to improve reproductive outcomes and metabolic parameters for women with PCOS and menstrual disturbance.

Risk of bias in included studies

No trials identified by the literature search were eligible for inclusion.

Effects of interventions

No trials identified by the literature search were eligible for inclusion.

DISCUSSION

The increasing prevalence and effects of pre-existing diabetes mellitus on maternal and infant health outcome highlight the importance of evaluating evidence-based management for these women both pre-conceptionally and during pregnancy. Additionally, women with impaired glucose tolerance or gestational diabetes in a previous pregnancy represent a group of women with relative insulin resistance, and are at risk of developing type 2 diabetes mellitus. Appropriate management of these women is unclear.

There were no data from randomised controlled trials evaluating the use of oral anti-diabetic agents for women with pre-existing diabetes mellitus, impaired glucose tolerance or previous gestational diabetes pre-conceptionally or for pregnant women with pre-existing diabetes that was able to be included in this review.

One trial published in 1971 (Notelovitz 1971) randomised women with gestational diabetes or type 2 diabetes mellitus to receive tolbutamide, chlorpropamide, insulin or diet alone. Although the study reported some maternal and infant health outcomes, data from women with type 2 diabetes and those with gestational diabetes were unable to be separated by the study site, and this precluded its inclusion in the review. Notelovitz and colleagues suggested, from the combined data, that the oral antidiabetic agents provided good glycaemic control without increases in perinatal mortality and congenital abnormality.

Given that the data were unable to be separated, these results from the trial could not be applied to women in this review.

Despite the limited evidence of the efficacy and safety of oral antidiabetic agents for women included in this review, the greater acceptability and potential compliance with oral antidiabetic agents suggest that further evidence is required. Large, high-quality randomised controlled trials evaluating the effects of oral anti-diabetic agents in women with pre-existing diabetes mellitus, impaired glucose tolerance or previous gestational diabetes mellitus planning pregnancy and pregnant women with pre-existing diabetes mellitus should include an assessment of maternal and infant health outcome, the adequacy of glycaemic control, women's views on the intervention and their health status and long-term health outcomes for mother and child. The combination of interventions will vary with type of diabetes or glucose intolerance, including comparisons between oral anti-diabetic agents, insulin therapy and dietary and lifestyle management.

One trial awaiting classification (Hutchinson 2008) randomised women with gestational diabetes or type 2 diabetes to insulin or a combination of glyburide and metformin and collected outcome data on maternal glycaemic control and maternal and infant health outcome. An additional trial is ongoing (Hague 2010), comparing metformin and placebo in women with a history of gestational diabetes and maternal and infant health outcome.

AUTHORS' CONCLUSIONS

Implications for practice

Little evidence is available evaluating the use of oral anti-diabetic agents in women with diabetes mellitus, impaired glucose tolerance or previous gestational diabetes mellitus planning a pregnancy or pregnant women with pre-existing diabetes mellitus. Current guidelines recommend the use of insulin in women with pre-existing diabetes mellitus, with the use of oral anti-diabetic agents considered on an individual basis.

Implications for research

Large, randomised controlled trials evaluating the use of oral antidiabetic agents in women with diabetes mellitus, impaired glucose tolerance or previous gestational diabetes mellitus planning a pregnancy or pregnant women with pre-existing diabetes mellitus. In particular, trials should compare oral antidiabetics with insulin or dietary and lifestyle control, and compare different oral antidiabetic agents. Outcomes reported should include maternal and infant health outcome, glycaemic control parameters, women's views on the intervention and long-term health outcomes for mother and child.

Acknowledgments

As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [*ordered by study ID*]

Study	Reason for exclusion
Anjalakshi 2007	Study evaluated treatment for women with gestational diabetes mellitus
Bertini 2005	Study evaluated treatment for women with gestational diabetes mellitus
Carlsen 2007	Study evaluated treatment for women with polycystic ovary syndrome
Golladay 2006	Study evaluated treatment for women with gestational diabetes mellitus
Hague 2003	Study evaluated treatment for women with gestational diabetes mellitus
Langer 2000	Study evaluated treatment for women with gestational diabetes mellitus
Moore 2005	Study evaluated treatment for women with gestational diabetes mellitus
Moore 2007	Study evaluated treatment for women with gestational diabetes mellitus
Notelovitz 1971	Original data for women with type 2 diabetes mellitus unable to be separated from data for women with gestational diabetes mellitus
Rowan 2008	Study evaluated treatment for women with gestational diabetes mellitus
Vanky 2004	Study evaluated treatment for women with polycystic ovary syndrome
Vanky 2006	Study evaluated treatment for women with polycystic ovary syndrome

Characteristics of studies awaiting assessment [*ordered by study ID*]

Hutchinson 2008

Methods	Randomised controlled trial. Funding: not specified.
Participants	Location: Chattanooga, Tennessee, United States. Inclusion criteria: women with gestational diabetes or type 2 diabetes mellitus not previously requiring insulin Exclusion criteria: none specified.
Interventions	Women were randomised to receive insulin or a glyburide/metformin regimen for glycaemic control. In both groups, women monitored blood glucose concentrations at home and were reviewed weekly. From 28 weeks' gestation, the women were seen twice weekly in addition to routine obstetric care
Outcomes	Primary outcomes: maternal haemoglobin A _{1c} , fructosamine, glucose at delivery. Secondary outcomes: mode of delivery, gestational age at delivery, infant birthweight, umbilical cord glucose, infant 1 hour glucose, infant complications (neonatal intensive care unit admissions, infant length of stay)
Notes	NCT00371306 No contributing data available at the moment.

Characteristics of ongoing studies [*ordered by study ID*]

Hague 2010

Trial name or title	Metformin in the prevention of gestational diabetes: the MPG trial
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Methods	Randomised controlled trial. Funding: Australian Diabetes Society, Merck Serono, Novo Nordisk Australia
Participants	Location: Adelaide, South Australia, Australia. Inclusion criteria: Women aged between 18 and 45 years old, with previously diagnosed gestational diabetes with a current viable, singleton pregnancy and gestational age from 12 weeks to 15 weeks and 6 days Exclusion criteria: known type 1, type 2 or current gestational diabetes, abnormal renal or liver function, hypoxic cardio-respiratory disease, malabsorption or significant gastro-intestinal disorder, excessive alcohol intake, recreational drug use in pregnancy, known fetal anomaly, multiple gestation
Interventions	Women are randomised to receive placebo or Metformin XR 500 mg daily. The dose is increased by one tablet per week up to four tablets daily (i.e. 2000 mg per day) as tolerated and continue on this dose until delivery
Outcomes Starting date	Primary outcome: diagnosis of gestational diabetes (by oral glucose tolerance test or high blood glucose levels on home blood glucose monitoring) at 26-28 weeks and 35-36 weeks Secondary outcomes: pregnancy hypertensive complication, composite neonatal outcome (neonatal hypogly-caemia, respiratory distress, need for phototherapy, birth trauma, 5 minute Apgar score < 7 and prematurity) , fetal macrosomia, neonatal adiposity Not yet known.
Contact information	Not yet known.
Notes	ACTRN12610000157077.

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 30 August 2010.

Date	Event	Description
10 January 2011	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 10, 2010

Date	Event	Description
2 December 2010	Amended	Corrected affiliation for Suzette Coat and William Hague.

References to studies excluded from this review

- Anjalakshi 2007 {published data only} . Anjalakshi C, Balaji V, Balaji MS, Seshiah V. A prospective study comparing insulin and glibenclamide in gestational diabetes mellitus in Asian Indian women. *Diabetes Research and Clinical Practice*. 2007; 76(3):474–5. [PubMed: 17113179]
- Bertini 2005 {published data only} . Bertini AM, Silva JC, Taborda W, Becker F, Bebbler FR, Viesi JM, et al. Perinatal outcomes and the use of oral hypoglycemic agents. *Journal of Perinatal Medicine*. 2005; 33(6):519–23. [PubMed: 16318615]

- Carlsen 2007 {published data only} . Carlsen SM, Kjøtrold S, Vanky E, Romundstad P. Homocysteine levels are unaffected by metformin treatment in both nonpregnant and pregnant women with polycystic ovary syndrome. *Acta Obstetrica et Gynecologica Scandinavica*. 2007; 86(2):145–50. [PubMed: 17364275]
- Golladay 2006 {published data only} . Golladay, EC. [accessed 21 March 2006] Glyburide compared to insulin in the management of White's classification A2 gestational diabetes. *ClinicalTrials.gov* [http://clinicaltrials.gov/](http://clinicaltrials.gov/ClinicalTrials.govhttp://clinicaltrials.gov/)
- Hague 2003 {published data only} . Hague WM, Davoren PM, Oliver J, Rowan J. Contraindications to use of metformin. Metformin may be useful in gestational diabetes. [comment]. *BMJ*. 2003; 326:762. author reply 762. [PubMed: 12680386]
- Langer 2000 {published data only} . Langer O, Conway D, Berkus M, Xenakis EMJ. Oral hypoglycaemic agent is comparable to insulin in GDM management. *American Journal of Obstetrics and Gynecology*. 1999; 180(1 Pt 2):S6.
- Langer O, Conway DL, Berkus MD, Xenakis EMJ, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *New England Journal of Medicine*. 2000; 343(16):1134–8. [PubMed: 11036118]
- Langer O, Yogev Y, Brustman L, Rosenn B. Is there a relationship between severity of gestational diabetes (gdm) and pregnancy outcome in insulin- and glyburide-treated patients [abstract]. *American Journal of Obstetrics and Gynecology*. 2003; 189(6 Suppl 1):S105.
- Langer O, Yogev Y, Rosenn B, Brustman L. Glyburide therapy: the relationship between dosage and level of gestational diabetes (gdm) severity [abstract]. *American Journal of Obstetrics and Gynecology*. 2003; 189(6 Suppl 1):S105.
- Langer O, Yogev Y, Xenakis EMJ, Rosenn B. Insulin and glyburide therapy: dosage, severity level of gestational diabetes, and pregnancy outcome. *American Journal of Obstetrics and Gynecology*. 2005; 192(1):134–9. [PubMed: 15672015]
- Letonturier P. [Gestational diabetes: an alternative to insulin therapy?]. [French]. *Presse Medicale*. 2001; 30:169–70.
- Moore 2005 {published data only} . Moore L, Clokey D, Robinson A. A randomized trial of metformin compared to glyburide in the treatment of gestational diabetes [abstract]. *American Journal of Obstetrics and Gynecology*. 2005; 193(6 Suppl):S92.
- Moore 2007 {published data only} . Moore L, Briery C, Martin R, Hood E, Bofill J, Morrison J. Metformin (M) vs. insulin (I) in A2 diabetes: a randomized clinical trial [abstract]. *American Journal of Obstetrics and Gynecology*. 2004; 191(6 Suppl 1):S8.
- Moore LE, Briery CM, Clokey D, Martin RW, Williford NJ, Bofill JA, et al. Metformin and insulin in the management of gestational diabetes mellitus: preliminary results of a comparison. *Journal of Reproductive Medicine*. 2007; 52(11):1011–5. [PubMed: 18161398]
- Notelovitz 1971 {published data only} . Notelovitz M. Sulphonylurea therapy in the treatment of the pregnant diabetic. *South African Medical Journal*. 1971; 45:226–9. [PubMed: 5121265]
- Rowan 2008 {published data only} . Rowan J. A trial in progress: gestational diabetes. *Diabetes Care*. 2007; 30:S214–9. [PubMed: 17596475]
- Rowan, J. [accessed 19 February 2008] Metformin in gestational diabetes: follow up of offspring of mothers treated with insulin compared with metformin. *Australian New Zealand Clinical Trials Registry*. www.anzctr.org.au
- Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, for the MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *New England Journal of Medicine*. 2008; 358(19):2003–15. [PubMed: 18463376]
- Vanky 2004 {published data only} . Salvesen KA, Vanky E, Carlsen SM. Metformin treatment in pregnant women with polycystic ovary syndrome - is reduced complication rate mediated by changes in the uteroplacental circulation? *Ultrasound in Obstetrics and Gynecology*. 2007; 29(4): 433–7. [PubMed: 17330831]
- Vanky, E.; Salvesen, KA.; Bjerve, K.; Carlsen, SM. C-Reactive protein in metformin treated pregnant PCOS women; XXXIV Congress of Nordic Federation of Societies of Obstetrics and Gynecology; Helsinki, Finland. 2004; Jun 12-15. p. 762004

- Vanky E, Salvesen KA, Heimstad R, Fougner KJ, Romundstad P, Carlsen SM. Metformin reduces pregnancy complications without affecting androgen levels in pregnant polycystic ovary syndrome women: results of a randomized study. *Human Reproduction*. 2004; 19(8):1734–40. [PubMed: 15178665]
- Vanky E, Salvesen KA, Hjorth-Hansen H, Bjerve K, Carlsen SM. Beneficial effect of metformin on pregnancy outcome in women with polycystic ovary syndrome is not associated with major changes in C-reactive protein levels or indices of coagulation. *Fertility & Sterility*. 2006; 85(3): 770–4. [PubMed: 16500361]
- Vanky 2006 {published data only} . Vanky, EI. [accessed 21 March 2006] Metformin in pregnant PCOS women (ongoing trial). *ClinicalTrials.gov*[http://clinicaltrials.gov/](http://clinicaltrials.gov/ClinicalTrials.govhttp://clinicaltrials.gov/)

References to studies awaiting assessment

- Hutchinson 2008 {published data only (unpublished sought but not used)} . Hutchinson A, Haugabrook C, Long L, Mason L, Kipikasa J, Adair D. A comparison of glyburide/metformin and insulin for gestational diabetes. *American Journal of Obstetrics and Gynecology*. 2008; 199(6 Suppl 1):S200.
- Kipikasa, JH. [accessed 20 February 2008] Comparison of glucovance to insulin for diabetes during pregnancy. *ClinicalTrials.gov*[http://clinicaltrials.gov/](http://clinicaltrials.gov/ClinicalTrials.govhttp://clinicaltrials.gov/)

References to ongoing studies

- Hague 2010 {published data only} . Hague, WM. [accessed 31 August 2010] Metformin in the prevention of gestational diabetes: the MPG trial. [http://www.anzctr.org.au/trial_view.aspx?ID=320961](http://www.anzctr.org.au/trial_view.aspx?ID=320961http://www.anzctr.org.au/trial_view.aspx?ID=320961) ACTRN12610000157077

Additional references

- ADA 2004 . American Diabetes Association. Preconception care of women with diabetes. *Diabetes Care*. 2004; 27(Suppl1):S76–S78. [PubMed: 14693933]
- ADIPS 2005 . McElduff A, Cheung NW, McIntyre HD, Lagstrom JA, Oats JJN, Ross GP, et al. The Australasian Diabetes in Pregnancy Society consensus guidelines for the management of type 1 and type 2 diabetes in relation to pregnancy. *Medical Journal of Australia*. 2005; 183(7):373–7. [PubMed: 16201957]
- Alwan 2009 . Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database of Systematic Reviews*. 2009; (3) DOI: 10.1002/14651858.CD003395.pub2.
- Bell 2008 . Bell R, Bailey K, Cresswell T, Hawthorne G, Critchley J, Lewis-Barned N, et al. Trends in prevalence and outcomes of pregnancy in women with pre-existing type I and type II diabetes. *BJOG: an international journal of obstetrics and gynaecology*. 2008; 115(4):445–52. [PubMed: 18271881]
- Brock 2005 . Brock B, Smidt K, Ovesen P, Schmitz O, Rungby J. Is metformin therapy for polycystic ovary syndrome safe during pregnancy? *Basic & Clinical Pharmacology & Toxicology*. 2005; 96:410–12. [PubMed: 15910403]
- Chan 2005 . Chan LYS, Yeung JHK, Lau TK. Placental transfer of rosiglitazone in the first trimester of human pregnancy. *Fertility and Sterility*. 2005; 83(4):955–8. [PubMed: 15820806]
- Coetzee 2007 . Coetzee EJ. Counterpoint: oral hypoglycemic agents should be used to treat diabetic pregnant women. *Diabetes Care*. 2007; 30:2980–2. [PubMed: 17965316]
- Cowie 2006 . Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, et al. Prevalence of diabetes and impaired fasting glucose in adults in the U.S. population: National Health And Nutrition Examination Survey 1999-2002. *Diabetes Care*. 2006; 29(6):1263–8. [PubMed: 16732006]

- Dabelea 2000 . Dabelea D, Knowler WC, Pettitt DJ. Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians. *Journal of Maternal-Fetal Medicine*. 2000; 9:83–8. [PubMed: 10757442]
- Damm 1995 . Damm P, Kuhl C, Hornnes P, Molsted-Pedersen L. A longitudinal study of plasma insulin and glucagon in women with previous gestational diabetes. *Diabetes Care*. 1995; 18(5): 654–65. [PubMed: 8586003]
- Deeks 2001 . Deeks, JJ.; Altman, DG.; Bradburn, MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger, M.; Davey Smith, G.; Altman, DG., editors. *Systematic reviews in health care: meta-analysis in context*. BMJ Books; London: 2001.
- DeFronzo 1984 . DeFronzo RA, Simonson DC. Oral sulfonylurea agents suppress hepatic glucose production in non-insulin-dependent diabetic individuals. *Diabetes Care*. 1984; 7(Suppl 1):72–80. [PubMed: 6428844]
- DeFronzo 1995 . DeFronzo RA, Goodman AM, the Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *New England Journal of Medicine*. 1995; 333(9):541–9. [PubMed: 7623902]
- Egger 1997 . Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315:629–34. [PubMed: 9310563]
- Ekpebegh 2007 . Ekpebegh CO, Coetzee EJ, Van der Merwe L, Levitt NS. A 10-year retrospective analysis of pregnancy outcome in pregestational type 2 diabetes: comparison of insulin and oral glucose-lowering agents. *Diabetic Medicine*. 2007; 24:253–8. [PubMed: 17305787]
- Gates 2005 . Gates, S.; The Editorial Team. Pregnancy and Childbirth Group. About the Cochrane Collaboration. Collaborative Review Groups (CRGs); 2005. Methodological Guidelines.
- Glueck 2004 . Glueck CJ, Goldenberg N, Pranikoff J, Lotspring M, Sieve L, Wang P. Height, weight, and motor-social development during the first 18 months of life in 126 infants born to 109 mothers with polycystic ovary syndrome who conceived on and continued metformin through pregnancy. *Human Reproduction*. 2004; 19(6):1323–30. [PubMed: 15117896]
- Gutzin 2003 . Gutzin SJ, Kozar E, Magee LA, Feig DS, Koren G. The safety of oral hypoglycemic agents in the first trimester of pregnancy: a meta-analysis. *Canadian Journal of Clinical Pharmacology*. 2003; 10(4):179–83. [PubMed: 14712322]
- Harbord 2006 . Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine*. 2006; 25:3443–57. [PubMed: 16345038]
- Hellmuth 2000 . Hellmuth E, Damm P, Molsted-Pedersen L. Oral hypoglycaemic agents in 118 diabetic pregnancies. *Diabetic Medicine*. 2000; 17(7):507–11. [PubMed: 10972579]
- Higgins 2009 . Higgins, JPT.; Green, S., editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]*. The Cochrane Collaboration; 2009. Available from www.cochrane-handbook.org
- Ho 2007 . Ho FLW, Liew CF, Cunanan EC, Lee KO. Oral hypoglycaemic agents for diabetes in pregnancy: an appraisal of the current evidence for oral anti-diabetic drug use in pregnancy. *Annals of the Academy of Medicine, Singapore*. 2007; 36:672–8.
- Homko 2006 . Homko CJ, Reece EA. Insulins and oral hypoglycemic agents in pregnancy. *Journal of Maternal-Fetal and Neonatal Medicine*. 2006; 19(11):679–86. [PubMed: 17127490]
- IDF 2009 . International Diabetes Federation. *IDF Diabetes Atlas*. 4th Edition. International Diabetes Federation; Brussels: 2009.
- Jensen 2004 . Jensen DM, Dam P, Moelsted-Pedersen L, Ovesen P, Westergaard JG, Moeller M, et al. Outcomes in type 1 diabetic pregnancies. *Diabetes Care*. 2004; 27(12):2819–23. [PubMed: 15562191]
- Jovanovic 2007 . Jovanovic L. Point: oral hypoglycemic agents should not be used to treat diabetic pregnant women. *Diabetes Care*. 2007; 30:2976–9. [PubMed: 17965315]
- Kim 2002 . Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2002; 25:1862–8. [PubMed: 12351492]
- Kim 2007 . Kim C, Berger DK, Chamany S. Recurrence of gestational diabetes mellitus: a systematic review. *Diabetes Care*. 2007; 30:1314–1319. [PubMed: 17290037]

- Kitzmler 1996 . Kitzmler JL, Buchanan TA, Kjos S, Combs CA, Ratner RE. Pre-conception care of diabetes, congenital malformations, and spontaneous abortions. *Diabetes Care*. 1996; 19(5): 514–41. [PubMed: 8732721]
- Kitzmler 2008 . Kitzmler JL, Block JM, Brown FM, Catalano PM, Conway DL, Coustan DR, et al. Managing preexisting diabetes for pregnancy: summary of evidence and consensus recommendations for care. *Diabetes Care*. 2008; 31(5):1060–79. [PubMed: 18445730]
- Kovo 2007 . Kovo M, Haroutinunian S, Feldman N, Hoffman A, Glezerman M. Determination of metformin transfer across the human placenta using a dually perfused ex vivo placental cotelydon model. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2008; 136(1):29–33. [PubMed: 17350747]
- Kraemer 2006 . Kraemer J, Klein J, Lubetsky A, Koren G. Perfusion studies of glyburide transfer across the human placenta: implications for fetal safety. *American Journal of Obstetrics and Gynecology*. 2006; 195(1):270–4. [PubMed: 16579925]
- Langer 2000 . Langer O, Conway DL, Berkus MD, Xenakis EMJ, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *New England Journal of Medicine*. 2000; 343(16):1134–8. [PubMed: 11036118]
- Lawrence 2008 . Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. *Diabetes Care*. 2008; 31(5):899–904. [PubMed: 18223030]
- Leguizamon 2007 . Leguizamon G, Igarzabal ML, Reece EA. Preconceptional care of women with diabetes mellitus. *Obstetrics and Gynecology Clinics of North America*. 2007; 34(2):225–39. [PubMed: 17572269]
- Macintosh 2006 . Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *BMJ*. 2006; 333(7560):177. [PubMed: 16782722]
- Meltzer 2003 . Meltzer, SJ.; Ryan, EA.; Feig, DS.; Thompson, D.; Snyder, J.; Canadian Diabetes Association. Clinical Practice Guidelines. Canadian Diabetes Association; 2003. Preconception care for women with diabetes.
- NICE 2008 . National Institute for Health and Clinical Excellence. Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE; London: 2008.
- Nissen 2007 . Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine*. 2007; 356:2457–71. [PubMed: 17517853]
- Ray 2001 . Ray JG, Vermeulen MJ, Shapiro JL, Kenshole AB. Maternal and neonatal outcomes in pregestational and gestational diabetes mellitus, and the influence of maternal obesity and weight gain: the DEPOSIT study. *Quarterly Journal of Medicine*. 2001; 94:347–56.
- RevMan 2008 . The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen: 2008.
- Rowan 2008 . Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, MiG Trial Investigators. Metformin versus insulin for the treatment of gestational diabetes. *New England Journal of Medicine*. 2008; 358(19):2003–15. [PubMed: 18463376]
- Seghieri 2007 . Seghieri G, Tesi F, Anichini R, De Bellis A, Barsotti E, Mari A, et al. Influence of gestational diabetes on the long-term control of glucose tolerance. *Diabetologia*. 2007; 50:2234–8. [PubMed: 17768604]
- Sheth 2002 . Sheth B. Does pregnancy accelerate the rate of progression of diabetic retinopathy? *Current Diabetes Report*. 2002; 23(8):327–30.
- Simonson 1984 . Simonson DC, Ferrannini E, Bevilacqua S, Smith D, Barrett E, Carlson R, et al. Mechanism of improvement of glucose metabolism after chronic glyburide therapy. *Diabetes*. 1984; 33(9):838–45. [PubMed: 6432610]
- Sivan 1995 . Sivan E, Feldman B, Dolitzki M, Nevo N, Dekel N, Karasik A. Glyburide crosses the placenta in vivo in pregnant rats. *Diabetologia*. 1995; 38(7):753–6. [PubMed: 7556974]

- Slocum 2002 . Slocum JM, Sosa MEB. Use of antidiabetes agents in pregnancy: current practice and controversy. *Journal of Perinatal and Neonatal Nursing*. 2002; 16(2):40–53. [PubMed: 12233944]
- Stumvoll 1995 . Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *New England Journal of Medicine*. 1995; 333(9):588–9. [PubMed: 7623910]
- Tang 2010 . Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. *Cochrane Database of Systematic Reviews*. 2010; (1) DOI: 10.1002/14651858.CD003053.pub4.
- Walkinshaw 2005 . Walkinshaw SA. Pregnancy in women with pre-existing diabetes: management issues. *Seminars in Fetal & Neonatal Medicine*. 2005; 10:307–15. [PubMed: 15927547]
- Weintrob 1996 . Weintrob N, Karp M, Hod M. Short- and long-range complications in offspring of diabetic mothers. *Journal of Diabetes and its Complications*. 1996; 10:294–301. [PubMed: 8887019]
- WHO 1999 . World Health Organization. Report of a WHO consultation: definition, diagnosis and classification of diabetes mellitus. WHO; Geneva: 1999.
- Yogev 2004 . Yogev Y, Langer O. The use of anti-hyperglycaemic and hypoglycaemic agents in pregnancy. *Fetal and Maternal Medicine Review*. 2004; 15(2):133–43.

* *Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

Oral anti-diabetic agents for women with pre-existing diabetes mellitus, impaired glucose tolerance or previous gestational diabetes mellitus

Pregnant women with type 1 or type 2 diabetes are at a greater risk of adverse outcomes in pregnancy, such as miscarriage or large babies and preterm birth. Being pregnant can trigger diabetes in women with impaired glucose tolerance or can accelerate the development of diabetic complications in women who are already diabetic. Women who have gestational diabetes are at risk of developing diabetes later in life. This means that management is important for women with diabetes and also for women with impaired glucose tolerance or previously diagnosed gestational diabetes.

It is usually recommended that women with diabetes have good control of their blood sugar levels before they become pregnant, and guidelines suggest insulin be used where additional control is required. Women with type 1 diabetes are likely to have used insulin for some time. Women with type 2 diabetes may have good control of their diabetes with diet and lifestyle changes alone, or with the use of an oral anti-diabetic agent. Women with diabetes using an oral anti-diabetic agent are usually advised to change to insulin before pregnancy for better blood sugar control and because there is little known about the effects of oral anti-diabetic agents in early pregnancy. Oral agents are, however, more convenient and acceptable than insulin injections and do not require the intensive education that is needed with insulin injections.

This review sought to investigate the effect of oral anti-diabetic agents in women with pre-existing diabetes mellitus, impaired glucose tolerance, or previous gestational diabetes, or women with diabetes mellitus planning a pregnancy on maternal and infant health.

We were not able to include any of the studies identified by the Cochrane literature search in the review. One trial has not been published in full yet and is awaiting assessment. An additional trial is ongoing. Further research is required comparing the effects of the oral antidiabetic agents with insulin and dietary and lifestyle advice in these women, in order to determine effects on the health of the mother and her baby, the level of blood sugar control achieved, women's views on the treatment, and long-term outcomes for the woman and child.