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Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes (Protocol)

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Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes.
Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD011967.
DOI: 10.1002/14651858.CD011967.

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[Intervention Protocol]

Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New, published in Issue 11, 2015.

Citation: Brown J, Martis R, Hughes B, Rowan J, Crowther CA. Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD011967. DOI: 10.1002/14651858.CD011967.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the effectiveness of oral agents in treating women with gestational diabetes for improving maternal and fetal health and well-being.

BACKGROUND

The original review by Alwan et al *Treatments for gestational diabetes* (Alwan 2009) has been split into three new review titles reflecting the complexity of treating women with gestational diabetes.

Lifestyle interventions for the treatment of women with gestational diabetes mellitus

Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes mellitus (this review)

Insulin for the treatment of women with gestational diabetes mellitus

There will be similarities in the background, methods and outcomes between these three systematic reviews. Portions of the methods section of this protocol are based on a standard template used by the Cochrane Pregnancy and Childbirth Review Group.

Description of the condition

Gestational diabetes mellitus (GDM) often referred to as gestational diabetes can be defined as 'glucose intolerance or hyperglycaemia (high blood glucose concentration) with onset or first recognition during pregnancy' (WHO 1999). GDM occurs when the body is unable to make enough insulin to meet the extra needs in pregnancy. The high blood sugars associated with GDM will return to normal after the birth of the baby. However, there is currently no universally accepted diagnostic criteria (ACOG 2013; Coustan 2010; HAPO 2008; Hoffman 1998; IADPSG 2010; Metzger 1998; NICE 2015). GDM may include previously undetected type 1 diabetes, type 2 diabetes or diabetes presenting only during pregnancy (HAPO 2008; IADPSG 2010; Metzger 1998; Nankervis 2014; WHO 2014).

GDM is one of the most common pregnancy complications and the prevalence is rising worldwide with 1% to 36% of pregnancies being affected (Bottalico 2007; Cundy 2014; Duran 2014;

Ferrara 2007; NICE 2015; Ragnarsdottir 2010; Tran 2013). The prevalence of GDM is likely to continue to increase along with the increasing prevalence of maternal obesity and associated type 2 diabetes (Bottalico 2007; Mulla 2010; Petry 2010).

A variety of factors have been associated with an increased risk of developing GDM. Non-modifiable risk factors include advanced maternal age (Chamberlain 2013; Morisset 2010), high parity, non-Caucasian race or ethnicity (in particular South Asian, Middle Eastern), family history of diabetes, maternal high or low birthweight, polycystic ovarian syndrome (Cypryk 2008; Petry 2010; Solomon 1997), a history of having a previous macrosomic infant (birthweight 4000 g or more) and previous history of GDM (Petry 2010).

Modifiable risk factors include physical inactivity (Chasan-Taber 2008), having a low-fibre and high-glycaemic load diet (Zhang 2006), maternal overweight (body mass index (BMI) equal to or greater than 25 kg/m^2) or obesity (equal to or greater than 30 kg/m^2) (Kim S 2010) and excessive weight gain during pregnancy, especially for those who are already overweight or obese (Hedderson 2010).

Pathophysiology of gestational diabetes

Normal pregnancy is associated with significant changes in maternal metabolism (Lain 2007). In early pregnancy, oestrogen and progesterone stimulate maternal beta-cell hyperplasia and insulin secretion, which promotes maternal nutrient storage (adipose and hepatic glycogen) to support later fetal growth. At this stage, insulin sensitivity is maintained or may even increase. However, as pregnancy progresses whole-body insulin sensitivity steadily decreases, such that by the third trimester it is reduced by almost half (Barbour 2007). Several factors contribute to this, including placental hormones (human placental lactogen and placental growth hormone), cytokines released from adipocytes (IL-6, TNF-alpha), increased free fatty acids and lower adiponectin concentrations (Clapp 2006; Devlieger 2008). This results in decreased post-prandial peripheral glucose disposal by up to 40% to 60% (Barbour 2007). Because glucose is transported to the fetus by facilitated diffusion, this state of physiological insulin resistance promotes fetal glucose uptake, a principal oxidative fuel and carbon source for the growing fetus. In normal pregnancy, maternal glycaemia is maintained by a significant increase in insulin secretion of up to 200% to 250% (Barbour 2007; Lain 2007; Suman Rao 2013).

Regulation of fetal glucose metabolism requires (1) the maintenance of maternal glucose concentration through increasing maternal glucose production, and at the same time, developing maternal glucose intolerance and insulin resistance, (2) transfer of glucose to the fetus across the placenta and (3) production of fetal insulin and uptake of glucose into adipose tissue and skeletal muscle (Suman Rao 2013).

Women with GDM have further reductions in insulin signalling, and glucose uptake is decreased beyond that of normal pregnancy (Barbour 2007). This results in glucose intolerance, though glycaemia in pregnancy represents a continuum. In GDM, the steeper maternal-fetal glucose gradient, especially post-prandial, leads to increased fetal glucose uptake which stimulates fetal insulin secretion. Insulin is a key fetal anabolic hormone and hyperinsulinaemia promotes fetal overgrowth leading to large-for-gestational age (LGA) infants, macrosomia, and possible organ damage (Catalano 2003; Ju 2008; Metzger 2008; Reece 2009).

Women with GDM also have increased circulating inflammatory cytokines and lower adiponectin concentrations leading to increased lipolysis and fatty acid concentrations. Placental transfer of free fatty acids contributes to increased fetal adiposity, independent of glucose uptake (Knopp 1985). Thus, even women with well-controlled GDM still have increased risk of fetal macrosomia (Langer 2005).

Screening and diagnosis of GDM

Regardless of whether universal or selective (risk-factor) screening with a 50 gram (g) oral glucose challenge test is used, diagnosis of GDM is usually based on either a 75 g two-hour oral glucose tolerance test (OGTT) or a 100 g three-hour OGTT (ADA 2013; IADPSG 2010; Nankervis 2014; NICE 2015; WHO 1999). Recommendations regarding diagnostic criteria vary nationally and internationally (Table 1), and these diagnostic criteria have changed over time, sometimes due to changing understanding about the effects of hyperglycaemia on pregnancy and infant outcomes (Coustan 2010), but also because of a lack of evidence clearly demonstrating the clinical and cost-effectiveness of one criterion over another.

The Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study (HAPO 2008), a large, international observational study reported graded linear associations in the odds of several GDM-associated adverse outcomes and glucose levels at OGTT, with no clear threshold identified at which risk increased substantially. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommended diagnostic criteria using data from the HAPO study (IADPSG 2010). Applying the IADPSG criteria in most health environments will increase the number of women with GDM. A study conducted in Vietnam showed that depending on the criteria used, the diagnosis of GDM varied between 5.9% (American Diabetes Association- ADA), 20.4% (International Association of Diabetes in Pregnancy Study Groups - IADPSG), 20.8% (Australasian Diabetes in Pregnancy Society - ADIPS), and up to 24.3% (World Health Organization - WHO) (Tran 2013). A Bulgarian study also reported differences in prevalence based on the diagnostic criteria ranging from 10.8% (European Association for the Study of Diabetes - EASD), 13.5% (ADA), 16.2% (New Zealand Society for the Study of Diabetes - NZSSD), 17.1% (WHO), 21.2% (ADIPS), 31.6% (IADPSG) (Boyadzhieva 2012).

Clinical outcomes for women with gestational diabetes

Adverse outcomes have been consistently reported at higher rates in women diagnosed with GDM and their infants compared to women without GDM (Crowther 2005; Landon 2009; Metzger 2008; Reece 2009).

Women with GDM have an increased risk of developing pre-eclampsia, are more likely to have their labour induced (Anderberg 2010; Crowther 2005; Ju 2008; Landon 2009; Metzger 2008), and giving birth by caesarean section (Landon 2009; Metzger 2008). The incidence of uterine rupture, shoulder dystocia and perineal lacerations are increased in women with GDM due to the increased likelihood of having a LGA or macrosomic baby (Jastrow 2010). Women who have experienced GDM are at a greater risk of metabolic dysfunction in later life (Shah 2008; Vohr 2008), with a crude cumulative incidence of type 2 diabetes of 10% to 20% within 10 years (Bellamy 2009; Kim 2002), but up to 50% when adjusted for retention and length of follow-up (Kim 2002).

Neonatal, infant and later outcomes related to gestational diabetes

A significant adverse health outcome for babies born to mothers with GDM is being born LGA or macrosomic (Catalano 2003; Crowther 2005; Landon 2009; Metzger 2008; Reece 2009). Large-for-gestational age or macrosomic infants are at increased risk of birth injury, such as shoulder dystocia, perinatal asphyxia, bone fractures and nerve palsies (Esakoff 2009; Henriksen 2008; Langer 2005; Metzger 2008).

Babies born to women with GDM, compared with babies born to women without GDM, have significantly greater skinfold measures and fat mass compared with infants of women with normal glucose tolerance (Catalano 2003). The offspring of women with GDM are heavier (adjusted for height) and have greater adiposity than the offspring of women with normal glycaemia during pregnancy (Pettitt 1985; Pettitt 1993), and are more likely to develop early overweight or obesity, type 2 diabetes (Hillier 2007; Pettitt 1993; Whincup 2008), or metabolic syndrome (a cluster of risk factors defined by the occurrence of three of the following: obesity, hypertension, hypertriglyceridaemia and low concentration of high-density lipoprotein (HDL) cholesterol) in childhood, adolescence or adulthood (Guerrero-Romero 2010; Harder 2009).

The development of the metabolic syndrome during childhood is a risk factor for the development of adult type 2 diabetes at 25 to 30 years of age (Morrison 2008). These health problems repeat across generations (Dabelea 2005; Mulla 2010) and are important from a public health perspective, because with each generation the prevalence of diabetes increases. Other adverse outcomes which are increased for babies born to women with GDM include respiratory distress syndrome, hypoglycaemia (which if prolonged can cause brain injury), hyperbilirubinaemia, hypertrophic cardiomyopathy, hypocalcaemia, hypomagnesaemia, polycythaemia and admission to the neonatal nursery (Metzger 2008; Reece 2009).

Description of the intervention

First-line treatment for women with gestational diabetes is usually a lifestyle intervention combining dietary and exercise components. Where glycaemic treatment targets are not attained by lifestyle interventions alone, or where initial glucose levels are considered to be very high, the option for treatment is to introduce a pharmacological intervention. Current options include subcutaneous insulin or oral anti-diabetic agents.

There has been an increase in the use of oral anti-diabetic agents as an alternative to subcutaneous insulin (Ogunyemi 2011) for the treatment of women with gestational diabetes, due to lower costs, ease of administration and acceptability (Ryu 2014). The most commonly used agents are glyburide (glibenclamide) and metformin, although there are other less frequently used anti-diabetic agents such as acarbose (Kalra 2015). Despite their wide use, oral antidiabetic agents are not licensed for use during pregnancy in many countries (including USA, UK, Australia, New Zealand).

First generation sulphonylureas such as chlorpropamide and tolbutamide have been used to treat diabetes in pregnancy in the past. Both drugs cross the placenta and have been associated with prolonged neonatal hypoglycaemia (Christesen 1998; Kemball 1970).

Second generation sulphonylureas such as glibenclamide (glyburide) or glipizide work by enhancing insulin secretion. In pregnancy, studies have focused on the use of glibenclamide as it was shown to have the least placental passage in vitro (Elliott 1991). However, with improved assays it is now estimated that cord plasma concentrations of glibenclamide can be 70% to 77% of maternal levels (Schwarz 2013). Glibenclamide is completely metabolised by the liver and the metabolites are excreted equally in bile and urine. Tablets are taken orally and the typical initial dose is 2.5 to 5 mg taken once a day. Dosage can be increased if glycaemic control is not achieved in increments of 2.5 mg daily at intervals of every seven days (Brayfield 2014). The maximum daily dose is usually 15 mg taken in divided doses. Glibenclamide is associated with weight gain during pregnancy and postpartum and maternal hypoglycaemia (Simmons 2014). Other commonly reported side effects include nausea, vomiting, sensations of fullness, abdominal pain, anorexia, heartburn and diarrhoea. Less common side effects include abnormal liver function, haematological reactions and dermatological reactions (http://www.medsafe.govt.nz). Glibenclamide is contraindicated in cases of renal and hepatic insufficiency (http://www.medsafe.govt.nz). A trial conducted by Langer 2000 reported equivalence between glyburide and subcutaneous insulin for the primary outcome of glycaemic control and reported that glibenclamide was not detected in the cord blood of any of the babies whose mother had been treated with glibenclamide in their trial.

Metformin is a biguanide that can be administered in immediate-release or sustained-release oral preparations. The drug is absorbed along the entire gastrointestinal mucosa, but absorption is incomplete. Typical doses and dose scheduling of metformin provide steady-state plasma concentrations within 24 to 48 hours of administration and are generally less than 1 microgram/mL. Metformin is excreted unchanged in the urine and is not metabolised by the liver. Tablets should be taken in divided doses with meals. The initial dose is typically 500 mg taken once or twice daily and may be increased over subsequent weeks, dependent on glycaemic control, up to a maximum of 1 g three times per day (http://www.medsafe.govt.nz). In clinical trials using metformin during pregnancy the maximum dose is 2500 g daily (Rowan 2008). Renal insufficiency is reported as a contra-indication to the prescription of metformin (http://www.fda.gov).

Metformin is known to cross the placenta although there is no evidence to suggest that this leads to fetal abnormalities (Ekpebegh 2007; Gilbert 2006). Maternal lactic acidosis is a rare (0.03 cases per 1000 patient years) but serious metabolic condition that is associated with accumulation of metformin during treatment (http://www.medsafe.govt.nz). Metformin is commonly associated with gastrointestinal disturbances (diarrhoea, nausea, vomiting) (Simmons 2014). Mild erythema, reduced vitamin B12 absorption and a metallic taste are also reported as side effects of metformin (http://www.medsafe.govt.nz). As very little metformin is transferred to human breast milk it is thought to be safe during breastfeeding (Simmons 2014). A sentinel trial conducted by Rowan 2008 reported equivalence between metformin and subcutaneous insulin for maternal and infant outcomes.

Combined metformin and glibenclamide - metformin and glibenclamide are available in some countries in a combined formulation (US, Europe).

Acarbose is a alpha-glucosidase inhibitor that delays the digestion of carbohydrates, thus resulting in a reduced increase in post-prandial blood glucose concentrations (http://www.accessdata.fda.gov). The typical initial dose is 75 to 150 mg taken in three divided doses. This can be further increased to a maximum of 600 mg per day (in divided doses) after four to eight weeks. Acarbose is metabolised within the gastrointestinal tract and the small amount that is excreted is via the urine (http://www.medsafe.govt.nz; http://www.accessdata.fda.gov). Animal studies have not found an association between acarbose and fetal teratogenicity, but data is lacking in human studies. (Kalra 2015). Acarbose is not associated with maternal hypoglycaemia but is frequently associated with gastrointestinal side effects (Simmons 2014). Acarbose is contraindicated in patients with inflammatory bowel disease or similar conditions, malabsorption syndromes, severe hepatic or renal impairment (http://www.medsafe.govt.nz).

Oral insulin is currently under research development for the treatment of diabetes mellitus, which may include gestational diabetes (Fonte 2013; Iyer 2010). This systematic review will not include trials of oral insulin as they will be included in the review of '*Insulin for the treatment of women with gestational diabetes*'.

How the intervention might work

Glibenclamide stimulates increased insulin secretion by binding to pancreatic beta-cell receptors. There is reduced basal hepatic glucose production and enhancement of peripheral insulin action at post-receptor (probably intracellular) sites. The mechanism of action of glibenclamide requires functional beta-cells (Patanè 2000). Glibenclamide also inhibits glucagon-producing alpha cells in the pancreas and increases the release of somatostatin. There is a mild diuretic action which increases free water clearance (Radó 1974).

Metformin actions are not completely understood but it inhibits glucogenesis in the liver, delays glucose absorption from the gastrointestinal tract and stimulates glucose uptake into the peripheral tissues. It has been suggested that as metformin increases insulin sensitivity, it does not stimulate insulin release, but does require the presence of insulin to potentiate its antihyperglycaemic effect. Both fasting and post-prandial blood glucose are lowered in individuals with diabetes as metformin does not stimulate insulin secretion it is not associated with an increase in hypoglycaemia in diabetic or non-diabetic populations. (http://www.medsafe.govt.nz). Metformin may protect β-cell function in the offspring and as a consequence reduce the cross generational effects of obesity and type 2 diabetes (Simmons 2014). During pregnancy the pharmacological action of metformin is altered slightly due to enhanced renal elimination, varying food absorption and gastrointestinal transit times (Simmons 2014).

Acarbose does not enhance insulin secretion. It reduces intestinal carbohydrate absorption by inhibiting the cleavage of disaccharides and oligosaccharides to monosaccharides in the small intestine resulting in reduced glucose absorption and lower post-prandial glucose concentrations (Kalra 2015).

Why it is important to do this review

Although oral anti-diabetic agents are more acceptable to women with GDM, cost less and are easier to administer than subcutaneous insulin, the safety of these drugs is still unclear.

The comparison of subcutaneous or oral insulin with oral anti-diabetic agents is the subject of a new Cochrane review and will not therefore be covered in this review.

Glibenclamide is associated with maternal weight gain, an association not seen with metformin and therefore any benefits in maternal glycaemic control may not be seen during the brief time available to treat women with gestational diabetes. The superiority of one anti-diabetic agent over another has not previously been addressed by a Cochrane systematic review.

OBJECTIVES

To evaluate the effectiveness of oral agents in treating women with gestational diabetes for improving maternal and fetal health and well-being.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published or unpublished randomised, quasi-randomised or cluster-randomised trials in full text or abstract format. We will exclude cross-over trials. Conference abstracts will be handled in the same way as full publications.

Types of participants

Participants will be pregnant women diagnosed with gestational diabetes (diagnosis as defined by the individual trial). Women with type 1 or type 2 diabetes diagnosed prior to pregnancy will be excluded.

Types of interventions

We will include those anti-diabetic agents that have been used during pregnancy including metfomin, glibenclamide, acarbose, tolbutamide, chlorpropamide or any combination of these agents. Only pharmacological agents will be included in this review. We will include any new agents prescribed for the treatment of women with GDM in updates of the review.

- Oral anti-diabetic agents versus placebo or no pharmacological treatment
- A single oral anti-diabetic agent versus an alternative oral anti-diabetic agent (drug A versus drug B)
- Any combination of oral anti-diabetic agents versus any combination of oral anti-diabetic agents (drug A followed by drug B versus drug B followed by drug A for example)
- Oral anti-diabetic agent versus another intervention (excluding insulin) not specified above

The comparison of oral anti-diabetic agents versus insulin has not been included in this review as it will be covered in the review entitled '*Insulin for the treatment of women with gestational diabetes*'.

Types of outcome measures

Primary outcomes

Maternal

- Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia as defined by trialists)
- Caesarean section
- Development of type 2 diabetes

Neonatal

- Perinatal (fetal and neonatal death) and later infant mortality
- Large-for-gestational age (LGA) (as defined by trialists)
- Death or serious morbidity composite (variously defined by trials, e.g. perinatal or infant death, shoulder dystocia, bone fracture or nerve palsy)
- Neurosensory disability in later childhood (as defined by trialists)

Secondary outcomes

Maternal

- Use of additional pharmacotherapy
- Maternal hypoglycaemia (as defined by trialists)
- Glycaemic control during/end of treatment (as defined by trialists)
- Weight gain in pregnancy
- Adherence to the intervention
- Induction of labour
- Placental abruption
- Postpartum haemorrhage (as defined by trialists)
- Postpartum infection
- Perineal trauma/tearing
- Breastfeeding at discharge, six weeks postpartum, six months or longer
- Maternal mortality
- Sense of well-being and quality of life
- Behavioural changes associated with the intervention
- Views of the intervention
- Relevant biomarker changes associated with the intervention (including adiponectin, free fatty acids, triglycerides, high-density lipoproteins, low-density lipoproteins, insulin)

Long-term outcomes for mother

- Postnatal depression
- Body mass index (BMI)
- Postnatal weight retention or return to pre-pregnancy weight
- Type 1 diabetes

- Type 2 diabetes
- Impaired glucose tolerance
- Subsequent gestational diabetes
- Cardiovascular health (as defined by trialists including blood pressure, hypertension, cardiovascular disease, metabolic syndrome)

Fetal/neonatal outcomes

- Stillbirth
- Neonatal death
- Macrosomia (greater than 4000 g; or as defined by individual study)
- Small-for-gestational age (SGA) (as defined by trialists)
- Birth trauma (shoulder dystocia, bone fracture, nerve palsy)
- Gestational age at birth
- Preterm birth (< 37 weeks' gestation; and < 32 weeks' gestation)
- Five-minute Apgar < seven
- Birthweight and z score
- Head circumference and z score
- Length and z score
- Ponderal index
- Adiposity (including skinfold thickness measurements (mm), fat mass)
- Neonatal hypoglycaemia (as defined by trialists)
- Respiratory distress syndrome
- Neonatal jaundice (hyperbilirubinaemia) (as defined by trialists)
- Hypocalcaemia (as defined by trialists)
- Polycythaemia (as defined by trialists)
- Relevant biomarker changes associated with the intervention (including insulin, cord c-peptide)

Later Infant/childhood outcomes

- Weight and z scores
- Height and z scores
- Head circumference and z scores
- Adiposity (including BMI, skinfold thickness, fat mass)
- Educational attainment
- Blood pressure
- Type 1 diabetes
- Type 2 diabetes
- Impaired glucose tolerance
- Dyslipidaemia or metabolic syndrome

Child as an adult outcomes

- Weight
- Height
- Adiposity (including BMI, skinfold thickness, fat mass)
- Cardiovascular health (as defined by trialists including blood pressure, hypertension, cardiovascular disease, metabolic syndrome)
- Employment, education and social status/achievement
- Dyslipidaemia or metabolic syndrome
- Type 1 diabetes
- Type 2 diabetes
- Impaired glucose tolerance

Health service use

- Number of antenatal visits or admissions
- Number of hospital or health professional visits (including midwife, obstetrician, physician, dietician, diabetic nurse)
- Admission to neonatal intensive care unit/nursery
- Length of antenatal stay
- Length of postnatal stay (maternal)
- Length of postnatal stay (baby)
- Cost of maternal care
- Cost of offspring care
- Costs associated with the intervention
- Costs to families associated with the management provided
- Cost of dietary monitoring (e.g. diet journals, dietician, nurse visits, etc)
- Costs to families - change of diet, extra antenatal visits
- Extra use of healthcare services (consultations, blood glucose monitoring, length and number of antenatal visits)
- Women's view of treatment advice
- Duration of stay in neonatal intensive care unit or special care baby unit
- Duration of maternal and neonatal hospital stay (antenatal, neonatal, postnatal)

Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);

5. handsearches of 30 journals and the proceedings of major conferences;

6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, 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.

In addition, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports. The search terms we plan to use are given in Appendix 1.

Searching other resources

We will search the reference lists of retrieved studies.

We will not apply any language or date restrictions.

Data collection and analysis

The following methods section of this protocol is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

We will create a study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2014) and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will 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 will assess the method as:

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

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

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

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will 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 will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention

a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will 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 will state whether attrition and exclusions were reported and 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 study authors, we will re-include missing data in the analyses which we undertake.
We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (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 risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Handbook* Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Assessment of the quality of the evidence using the GRADE approach

The quality of the evidence will be assessed using the GRADE approach as outlined in the GRADE Handbook in order to assess the quality of the body of evidence relating to the following outcomes. We have selected up to a maximum of seven outcomes for the mother and seven for the infant covering both short- and long-term outcomes for the main comparisons.

Maternal outcomes

- Hypertensive disorders of pregnancy (including pre-eclampsia, pregnancy-induced hypertension, eclampsia)
- Caesarean section
- Development of type 2 diabetes
- Perineal trauma
- Return to pre-pregnancy weight
- Postnatal depression
- Induction of labour

Neonatal outcomes

- LGA
- Perinatal mortality
- Death or morbidity composite (variously defined by studies, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy)
- Neonatal hypoglycaemia
- Adiposity
- Diabetes
- Neurosensory disability

We will use the GRADEpro Guideline Development Tool to import data from Review Manager (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by

two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will 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 will include cluster-randomised trials in the analyses along with individually-randomised trials. We will make adjustments using the methods described in the *Handbook* [Section 16.3.4 or 16.3.6] using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. We will consider it reasonable to combine the results from both cluster-randomised trials and individually-randomised trials 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. If cluster-randomised trials are included, we will seek statistical advice on appropriate analysis to enable inclusion of data in the meta-analyses.

Other unit of analysis issues

Multiple pregnancy

There may be unit of analysis issues that arise when the women randomised have a multiple pregnancy. We will present maternal data as per woman randomised and neonatal data per infant.

Multiple-arm studies

Where a trial has multiple intervention arms we will avoid 'double counting' of participants by combining groups to create a single pair-wise comparison if possible. Where this is not possible, we will split the 'shared' group into two or more groups with smaller sample size and include two or more (reasonably independent) comparisons.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data (> 20%) in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a Tau^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 are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary

will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.
If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

Diagnostic test used

- ADA 2013, IADPSG 2010, Nankervis 2014 versus ACOG 2013 versus NICE 2015 versus NICE 2008; WHO 1999; WHO 2014; Hoffman 1998 versus New Zealand Ministry of Health 2014 versus other not previously specified

Timing of diagnosis

- Early (< 28 weeks' gestation) versus late (≥ 28 weeks' gestation)

The following outcomes will be used in subgroup analysis.
Maternal outcomes

- Pre-eclampsia
- Caesarean section
- Development of type 2 diabetes

Neonatal outcomes

- LGA
- Perinatal mortality
- Death or morbidity composite (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy)
- Neurosensory disability in later childhood (as defined by trialists).

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

If there is evidence of substantial heterogeneity, we will explore this by using the quality of the included trials for the primary outcomes. We will compare trials that have low risk of bias for allocation concealment with those judged to be of unclear or high risk of bias, and conference abstracts will be excluded from the meta-analysis.
We will also investigate the effect of the randomisation unit (i.e. where include cluster-randomised trials along with individually-randomised trials).

ACKNOWLEDGEMENTS

We acknowledge the valuable contributions of Nisreen Alwan, Jane West and Derek Tuffnall who were the authors of the original review *Treatments for gestational diabetes* (Alwan 2009).

We acknowledge the contribution of the authors of the other two reviews that were split from this original review in the preparation of the core background sections of the new review protocols.

Lifestyle interventions for the treatment of women with gestational diabetes - Julie Brown, Nisreen Alwan, Stephen Brown, Christopher McKinlay, Diane Farrar, Jane West, Caroline Crowther.

Insulin for the treatment of women with gestational diabetes - Julie Brown, Luke Greskowiak, Michelle Downie, Kate Williamson, Caroline Crowther.

We acknowledge the support from the Cochrane Pregnancy and Childbirth Review Group editorial team in Liverpool, the Australian and New Zealand Satellite of the Cochrane Pregnancy and Childbirth Review Group and the Liggins Institute, University of Auckland, New Zealand.

As part of the pre-publication editorial process, this protocol has been commented on by five peers (an editor and four referees who are external to the editorial team) and the Group's Statistical Adviser.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure and Cochrane Programme Grant funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Examples of diagnostic criteria for gestational diabetes

Organisation/ professional body	Screening and diagnostic criteria					
	One-hour oral glucose challenge test	Oral glucose tolerance test	Fasting	One hour	Two hour	Three hour
ADA 2013* , IADPSG 2010*, ADIPS 2013 (Nankervis 2014)	-	75 g	≥ 5.1 mmol/L (≥ 92 mg/dL)	≥ 10 mmol/L (≥ 180 mg/dL)	≥ 8.5 mmol/L (≥ 153 mg/dL)	-

Table 1. Examples of diagnostic criteria for gestational diabetes (*Continued*)

; WHO 2014						
ACOG 2013 Carpenter and Coustan^	50 g (> 7.2 mmol/L; > 130 mg/dL)	100 g	≥ 5.3 mmol/L (95 mg/dL)	≥ 10 mmol/L (180 mg/dL)	≥ 8.6 mmol/L (155 mg/dL)	≥ 7.8 mmol/L (140 mg/dL)
National Diabetes Data Group^	50 g (> 7.8 mmol/L; > 140 mg/dL)	100 g	≥ 5.8 mmol/L (105 mg/dL)	≥ 10.6 mmol/L (190 mg/dL)	≥ 9.2 mmol/L (165 mg/dL)	≥ 8.0 mmol/L (145 mg/dL)
Canadian Diabetes Association 2013 either* or^	50 g -	75 g 75 g	≥ 5.3 mmol/L (95 mg/dL) ≥ 5.1 mmol/L (≥ 92 mg/dL)	≥ 10.6 mmol/L (190 mg/dL) ≥ 10 mmol/L (≥ 180 mg/dL)	≥ 9.0 mmol/L ≥ 8.5 mmol/L (≥ 153 mg/dL)	
NICE 2015	-	75 g	≥ 5.6 mmol/L (≥ 101 mg/dL)	-	≥ 7.8 mmol/L (140 mg/dL)	-
NICE 2008; WHO 1999; Hoffman 1998 (ADIPS)^	-	75 g	≥ 7.0 mmol/L (≥ 126 mg/dL)	-	≥ 11.1 mmol/L (≥ 200 mg/dL)	-
New Zealand Ministry of Health 2014*	50 g if HbA1c < 41 mmol/mol (≥ 7.8 mmol/L; ≥ 140 mg/dL)	75 g	≥ 5.5 mmol/L (≥ 99 mg/dL)	-	≥ 9.0 mmol/L (≥ 162 mg/dL)	-

ADA American Diabetes Association
IADPSG International Association of the Diabetes and Pregnancy Study Groups
ADIPS Australasian Diabetes in Pregnancy Society
ACOG American College of Obstetrics and Gynecology
NICE National Institute for Health and Care Excellence
*1 abnormal result required for diagnosis
^2 or more abnormal results required for diagnosis

APPENDICES

Appendix 1. Trial registry search strategy

ClinicalTrials.gov and WHO ICTRP
Search terms: oral anti-diabetic OR oral hypoglycaemic* OR oral hypoglycemic* OR metformin OR glibenclamide OR glyburide OR acarbose AND gestational diabetes OR GDM
(Each term for medication will be combined separately with each term for gestational diabetes)

CONTRIBUTIONS OF AUTHORS

Julie Brown guarantees this protocol.

Julie Brown wrote the first version of this protocol and all authors have contributed to subsequent versions.

DECLARATIONS OF INTEREST

Julie Brown: none known

Ruth Martis: none known

Brenda Hughes: none known

Janet Rowan has been involved with the study of metformin in pregnancy, as the Principal Investigator (PI) in a trial (the Mig Trial) that may be considered for inclusion in this review. She has also been the PI in the offspring follow up studies (TOFU). These trials were run according to good clinical practice guidelines and the results will be presented according to the findings of the trial. Janet Rowan will not be involved in any decisions (inclusion/exclusion, risk of bias, quality assessment or data extraction) relating to her own trials in this Cochrane review.

Caroline A Crowther: none known

SOURCES OF SUPPORT

Internal sources

- An internal University department grant, New Zealand.

An internal University of Auckland department grant from the Liggins Institute has been awarded to Julie Brown to help with the preparation of several Cochrane systematic reviews as part of an overview of systematic reviews for the treatment of women with gestational diabetes. This current protocol/review will be one of the included reviews.

- Liggins Institute, New Zealand.

Support for infrastructure to support the preparation of this protocol is from the Liggins Institute, University of Auckland, New Zealand.

External sources

- No sources of support supplied

NOTES

The original review by Alwan et al (Alwan 2009) has been split into three new reviews due to the complexity of the included interventions. The following new review protocols are underway.

Lifestyle interventions for the treatment of women with gestational diabetes mellitus

Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes mellitus (this review)

Insulin for the treatment of women with gestational diabetes mellitus