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Insulin for the treatment of women with gestational diabetes (Protocol)

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[Intervention Protocol]

Insulin for the treatment of women with gestational diabetes

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ABSTRACT

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

To evaluate the effects of insulin in treating women with gestational diabetes.

BACKGROUND

The original review by Alwan 2009 has been split into three new reviews due to the complexity of the included interventions. The new review protocols include the following.

Lifestyle interventions for the treatment of women with gestational diabetes (Brown 2015a)

Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes (Brown 2015b)

Insulin for the treatment of women with gestational diabetes (this protocol).

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 usually return to normal after the birth of the baby. However, there is currently no universally accepted diagnostic criteria (ACOG 2013; ADA 2013, Coustan 2010; HAPO 2008; Hoffman 1998; IADPSG 2010; Metzger 1998; NICE 2015) (Table 1). GDM may include previously undetected type 1 diabetes, type 2 diabetes, or diabetes presenting only during pregnancy depending on when the timing of when diagnosis is made (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 ;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 mellitus (Bottalico

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2007; Mulla 2010; Petry 2010).

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 performed between 24 and 28 weeks' gestation (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) was a large, international observational study which 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 diagnosed 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).

Pathophysiology of gestational diabetes mellitus

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). 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).

Risk factors associated with gestational diabetes mellitus

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 mellitus, 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 a 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).

Clinical outcomes for women with pregnancy hyperglycaemia

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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 are more likely to give birth by caesarean section (Landon 2009; Metzger 2008). The incidence of uterine rupture, shoulder dystocia and perineal lacerations is 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 pregnancy hyperglycaemia

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 1993; Pettitt 1985) 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 a 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

While women with gestational diabetes still make insulin, their bodies are insensitive to it and do not produce enough insulin to maintain glycaemic control. Insulin is often the treatment of choice for women who are unable to maintain glycaemic treatment targets with medical nutrition therapy or other pharmacological therapies (NICE 2015). Insulin may be an alternative for women who are unable to tolerate the side effects (gastrointestinal upset for example) of oral anti-diabetic pharmacological therapies such as metformin. Glycaemic control is maintained by the replacement of insulin, which facilitates the transport of glucose from the blood stream into the cells of the body for energy. Insulin in itself describes a group of heterogeneous preparations that are clinically differentiated by their course of action over time. Rapid-acting or short-acting insulin is used to mimic the response of endogenous insulin to food intake and is useful in correcting post-prandial hyperglycaemia, without causing pre-prandial hypoglycaemia (bolus insulin) (Lambert 2013; Negrato 2012). In contrast, intermediate-acting and long-acting insulin is primarily used to provide a continuous supply of small amounts of insulin independent of food intake, over a longer period of time, which regulates lipolysis and the output of hepatic glucose (basal insulin) (Lambert 2013; Negrato 2012). At normal therapeutic doses all types of insulin do not cross the placenta (Lambert 2013; Negrato 2012).

Types of insulin used during pregnancy

Rapid-acting insulin

Insulin lispro, aspart and glulisine are commonly used rapid-acting insulin analogues. Their onset of action is within 15 minutes or less following administration. Peak concentrations are reached between 30 to 80 minutes and the maximum duration of action is between three to six hours (Lambert 2013; Negrato 2012).

Short-acting insulin

Regular human insulin - has an onset of action between 30 to 60 minutes and a time to peak concentration of 90 to 120 minutes with a maximum duration of action of five to 12 hours (Lambert 2013).

Intermediate-acting insulin

Neutral protamine Hagedorn (NPH) insulin, also known as isophane insulin is a longer acting form of regular human insulin, it has an onset of action of about 60 to 120 minutes and a time to peak action of 240 to 480 minutes. The maximum duration of action is about 16 to 18 hours (Lambert 2013).

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Long-acting insulin

Insulin detemir - this analogue has an onset of action about 60 to 120 minutes after administration and action lasts for 18 to 20 hours. There is no peak of action (Negrato 2012).
Insulin glargine - this analogue has an onset of action about 60 to 120 minutes after administration and action lasts for 24 hours. There is no peak of action (Negrato 2012).
Pre-mixed insulin - contains a mixture of rapid-acting or short-acting insulin with intermediate-acting insulin. Provides a more rapid onset of action with a subsequent peak and prolonged duration of action.

Other formulations of insulin

Pharmaceutical companies are currently working on other routes of administration of insulin including inhaled and oral. These are still in early trial phases and may be available in the future. Newer analogues of ultra-long insulin are also being introduced.

Insulin regimens

As a result of the numerous types of insulin available, various regimens for insulin administration may be utilised. This may take the form of multiple injections throughout the day, or continuous administration by subcutaneous insulin infusion. The optimal insulin replacement regimen should be viewed in light of the need to provide appropriate basal insulin requirements across 24 hours, provide sufficient levels to cover food intake, have adequate provision for correction of blood glucose levels when needed, minimise blood glucose fluctuations, and therefore risk of hypoglycaemia and hyperglycaemia, and achieve optimal pregnancy outcomes. Insulin can be administered as:

- a once-daily dose which involves taking a single dose of insulin (intermediate or long-acting insulin) each day. Individuals may also take oral anti-diabetic drugs in addition to insulin.
- a twice-daily regimen (basal-plus) which involves adding in one or two doses of rapid-acting insulin on to an intermediate or basal dose.
- a basal-bolus regimen which involves taking a long-acting or intermediate-acting dose and then separate injections of short- or rapid-acting insulin at each meal. This regimen is more common in those with type 1 diabetes. An advantage of this regimen is that it offers flexibility over timing of meals and variations based on different carbohydrate quantities in meals.
- a continuous subcutaneous infusion which involves delivery of a consistent amount of rapid-acting insulin via an insulin pump. At meal times a bolus of insulin can be delivered to maintain glycaemic control.

How the intervention might work

Insulin is a pancreatic hormone that regulates the movement of glucose from blood into cells. Insulin lowers blood glucose by stimulating peripheral glucose uptake and by inhibiting glucose production and release by the liver. Insulin inhibits lipolysis (breakdown of fat), proteolysis (breakdown of proteins), and gluconeogenesis (manufacture of glucose). It also increases protein synthesis and conversion of excess glucose into fat (Girard 2006).

Why it is important to do this review

With the rising prevalence of gestational diabetes (Bottalico 2007; Mulla 2010), it is likely that more women will require pharmacotherapy to maintain glycaemic control during their pregnancy to reduce the associated maternal and neonatal short- and long-term effects of gestational diabetes. Adherence to medication is an important aspect of treatment for gestational diabetes (NICE 2015). Oral anti-diabetic agents may be an alternative to insulin. As more insulin analogues emerge on the market, it is important to establish their safety and efficacy for pregnant women with gestational diabetes and to identify the optimal regimen for administering insulin. This review will attempt to answer these important questions.

OBJECTIVES

To evaluate the effects of insulin in treating women with gestational diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

We will include published or unpublished randomised or cluster-randomised trials in full text or abstract format. We will exclude quasi-randomised studies and cross-over trials.

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.

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Types of interventions

We will consider the following interventions and comparisons.

- Insulin (any type) versus oral anti-diabetic agents
- Insulin (any type) versus diet
- Insulin (any type) versus exercise
- Insulin (any type) versus diet plus exercise
- Insulin (any type) versus other treatment intervention not previously described
- Insulin type A versus insulin type B (e.g. rapid-acting versus short-acting; intermediate-acting versus long-acting insulin)
- Insulin regimen A versus insulin regimen B

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 (as defined by trialists, including results of postnatal testing)

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 (HDL), low-density lipoproteins (LDL), 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)

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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
- Duration of stay in neonatal intensive care unit or special care baby unit
- 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

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 search Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator.

For full search methods used to populate the PCG Trials Register including the detailed 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, please follow this link to the editorial information about the Cochrane Pregnancy and Childbirth Group in *The Cochrane Library* and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, 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.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth Group review topic (or topics), and is then added to the Register. The Trials Search Co-ordinator searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using search terms detailed 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

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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 trial 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.

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(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.

Assessing the quality of the body of 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/offspring covering both short- and long-term outcomes for the main comparisons.

Maternal outcomes

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

Neonatal/child/adult outcomes

1. LGA
2. Perinatal mortality
3. Death or morbidity composite (variously defined by studies, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy)
4. Neonatal hypoglycaemia
5. Adiposity
6. Diabetes
7. Neurosensory disability

We will use the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (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

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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. When 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 2008; WHO 1999; WHO 2014; Hoffman 1998 versus New Zealand Ministry of Health 2014 versus other not previously specified.

Timing of diagnosis

Early diagnosis (< 28 weeks' gestation) versus late diagnosis (≥ 28 weeks' gestation).

Comparator intervention

Metformin versus glibenclamide versus acarbose versus diet alone versus exercise alone versus diet plus exercise versus other intervention (not previously specified).

The following outcomes will be used in subgroup analysis.

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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 significant 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. We will exclude conference abstracts.

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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:

- Oral anti-diabetic pharmacological therapies for the treatment of women with gestational diabetes - Julie Brown, Ruth Martis, Brenda Hughes, Janet Rowan, Caroline Crowther.
- Lifestyle interventions for the treatment of women with gestational diabetes - Julie Brown, Nisreen Alwan, Jane West, Stephen Brown, Christopher McKinlay, Dianne Farrar, Caroline Crowther.

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As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

REFERENCES

Additional references

ACOG 2013
American College of Obstetricians and Gynecologists Committee on Practice Bulletins--Obstetrics. ACOG Practice Bulletin No. 137: Gestational diabetes mellitus, August 2013 (replaces practice bulletin number 30, September 2001; Committee Opinion Number 435, June 2009 and Committee Opinion Number 504, September 2011). *Obstetrics & Gynecology* 2013;**122**(2 Pt 1):406–16.

ADA 2013
American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2013;**36**(Suppl 1): 567–74.

Anderberg 2010
Anderberg E, Kallen K, Berntorp K. The impact of gestational diabetes mellitus on pregnancy outcome comparing different cut-off criteria for abnormal glucose tolerance. *Acta Obstetricia et Gynecologica Scandinavica* 2010;**89**(12):1532–7.

Barbour 2007
Barbour LA, McCurdy CE, Hernandez TL, Kirwan JP, Catalano PM, Friedman JE. Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care* 2007;**30**(Suppl 2):S111–S119.

Bellamy 2009
Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 2009;**373**(9677):1173–9.

Bottalico 2007
Bottalico JN. Recurrent gestational diabetes: risk factors, diagnosis, management, and implications. *Seminars in Perinatology* 2007;**31**(3):176–84.

Boyadzhieva 2012
Boyadzhieva MV, Atanasova I, Zacharieva S, Tankova T,

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Dimitrova V. Comparative analysis of current diagnostic criteria for gestational diabetes mellitus. *Obstetric Medicine* 2012;**5**:71–7.

Brown 2015a

Brown J, Alwan NA, West J, Brown S, McKinlay CJD, Farrar D, et al. Lifestyle interventions for the treatment of women with gestational diabetes. *Cochrane Database of Systematic Reviews* 2015, Issue 11. [DOI: 10.1002/14651858.CD011970]

Brown 2015b

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. [DOI: 10.1002/14651858.CD011967]

Catalano 2003

Catalano PMA, Huston-Presley TL, Amini SB. Increased fetal adiposity: a very sensitive marker of abnormal in utero development. *American Journal of Obstetrics & Gynecology* 2003;**189**(6):1698–704.

Chamberlain 2013

Chamberlain C, McNamara B, Williams E, Yore D, Oldenburg B, Oats J, et al. Diabetes in pregnancy among indigenous women in Australia, Canada, New Zealand and the United States. *Diabetes/metabolism Research and Reviews* 2013;**29**(4):241–56.

Chasan-Taber 2008

Chasan-Taber L, Schmidt MD, Pekow P, Sternfeld B, Manson JE, Solomon CG, et al. Physical activity and gestational diabetes mellitus among Hispanic women. *Journal of Women's Health* 2008;**17**(6):999–1008.

Clapp 2006

Clapp JF. Effects of diet and exercise on insulin resistance during pregnancy. *Metabolic Syndrome and Related Disorders* 2006;**4**(2):84–90.

Coustan 2010

Coustan DR, Lowe LP, Metzger BE, Dyer AR, International Association of Diabetes and Pregnancy Study Groups. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study: paving the way for new diagnostic criteria for gestational diabetes mellitus. *American Journal of Obstetrics & Gynecology* 2010;**202**(6):654.e1–6.

Crowther 2005

Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, et al. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *New England Journal of Medicine* 2005;**352**(24):2477–86.

Cundy 2014

Cundy T, Ackermann E, Ryan EA. Gestational diabetes: new criteria may triple the prevalence but effect on outcomes is unclear. *BMJ* 2014;**348**:g1567.

Cypryk 2008

Cypryk K, Szymczak W, Czupryniak L, Sobczak M, Lewinski A. Gestational diabetes mellitus - an analysis of risk factors. *Endokrynologia Polska (Warszawa)* 2008;**59**(5):393–7.

Dabelea 2005

Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS, et al. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. *Diabetes Care* 2005;**28**(3):579–84.

Devlieger 2008

Devlieger R, Casteels K, Van Assche FA. Reduced adaptation of the pancreatic B cells during pregnancy is the major causal factor for gestational diabetes: current knowledge and metabolic effects on the offspring. *Acta Obstetricia et Gynecologica Scandinavica* 2008;**87**(12):1266–70.

Duran 2014

Duran A, Saenz S, Torrejon M, Bordiu E, del Valle L, Galindo M, et al. Introduction of IADPSG criteria for the screening and diagnosis of gestational diabetes mellitus results in improved pregnancy outcomes at a lower cost in a large cohort of pregnant women: the St. Carlos Gestational Diabetes Study. *Diabetes Care* 2014;**37**:2442–50.

Esakoff 2009

Esakoff TF, Cheng YW, Sparks TN, Caughey AB. The association between birthweight 4000 g or greater and perinatal outcomes in patients with and without gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology* 2009;**200**(6):672.e1–672.e4.

Ferrara 2007

Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care* 2007;**30**(Suppl 2):S141–S146.

Girard 2006

Girard J. The inhibitory effects of insulin on hepatic glucose production are both direct and indirect. *Diabetes* 2006;**55**(Suppl 2):S65–S69.

Guerrero-Romero 2010

Guerrero-Romero F, Aradillas-García C, Simental-Mendia LE, Monreal-Escalante E, De la Cruz Mendoza E, Rodríguez-Moran M. Birth weight, family history of diabetes, and metabolic syndrome in children and adolescents. *Journal of Pediatrics* 2010;**156**(5):719–23.

HAPO 2008

The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine* 2008;**358**:1991–2002.

Harder 2009

Harder T, Roepke K, Diller N, Stechling Y, Dudenhausen JW, Plagemann A. Birth weight, early weight gain, and subsequent risk of type 1 diabetes: systematic review and meta-analysis. *American Journal of Epidemiology* 2009;**169**(12):1428–36.

Hedderson 2010

Hedderson MM, Gunderson EP, Ferrara A. Gestational weight gain and risk of gestational diabetes mellitus. *Obstetrics & Gynecology* 2010;**115**(3):597–604.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Henriksen 2008
Henriksen T. The macrosomic fetus: a challenge in current obstetrics. *Acta Obstetricia et Gynecologica Scandinavica* 2008;**87**(2):134–45.

Higgins 2011
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hillier 2007
Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care* 2007;**30**(9):2287–92.

Hoffman 1998
Hoffman L, Nolan C, Wilson JD, Oats JJ, Simmons D. The Australasian Diabetes in Pregnancy Society. Gestational diabetes mellitus-management guidelines. *Medical Journal of Australia* 1998;**169**(2):93–7.

IADPSG 2010
International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. *Diabetes Care* 2010;**33**(3): 676–82.

Jastrow 2010
Jastrow N, Roberge S, Gauthier RJ, Laroche L, Duperron L, Brassard N, et al. Effect of birth weight on adverse obstetric outcomes in vaginal birth after cesarean delivery. *Obstetrics & Gynecology* 2010;**115**(2 Pt 1):338–43.

Ju 2008
Ju H, Rumbold AR, Willson KJ, Crowther CA. Effect of birth weight on adverse obstetric outcomes in vaginal birth after caesarean delivery. *BMC Pregnancy and Childbirth* 2008;**8**:31.

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.

Kim S 2010
Kim SY, England L, Wilson HG, Bish C, Satten GA, Dietz P. Percentage of gestational diabetes attributable to overweight and obesity. *American Journal of Public Health* 2010;**100**(6):1047–52.

Knopp 1985
Knopp RH, Bergelin RO, Wahl PW, Walden CE. Relationships of infant birth size to maternal lipoproteins, apoproteins, fuels, hormones, clinical chemistries, and body weight at 36 weeks gestation. *Diabetes* 1985;**34**(Suppl 2): 71–7.

Lain 2007
Lain KY, Catalano PM. Metabolic changes in pregnancy. *Clinical Obstetrics and Gynecology* 2007;**50**(4):938–48.

Lambert 2013
Lambert K, Holt RIG. The use of insulin analogues in pregnancy. *Diabetes, Obesity and Metabolism* 2013;**15**: 888–900.

Landon 2009
Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *New England Journal of Medicine* 2009;**361**(14):1339–48.

Langer 2005
Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. *American Journal of Obstetrics and Gynecology* 2005;**192**(4):989–97.

Metzger 1998
Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 1998;**21** (Suppl 2):B161–B167.

Metzger 2008
Metzger B, for The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine* 2008;**358**:1991–2002.

Ministry of Health 2014
Ministry of Health. *Screening, Diagnosis and Management of Gestational Diabetes in New Zealand: A Clinical Practice Guideline*. Wellington: Ministry of Health, 2014.

Morisset 2010
Morisset AS, St-Yves A, Veillette J, Weisnagel SJ, Tchernof A, Robitaille J. Prevention of gestational diabetes mellitus: a review of studies on weight management. *Diabetes/ Metabolism Research and Reviews* 2010;**26**(1):17–25.

Morrison 2008
Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years late. *Journal of Pediatrics* 2008;**152**(2):201–6.

Mulla 2010
Mulla WR, Henry TQ, Homko CJ. Gestational diabetes screening after HAPO: has anything changed?. *Current Diabetes Reports* 2010;**10**(3):224–8.

Nankervis 2014
Nankervis A, McIntyre HD, Moses R, Ross GP, Callaway L, Porter C, et al. ADIPS consensus guidelines for the testing and diagnosis of hyperglycaemia in pregnancy in Australia and New Zealand. http://adips.org/downloads/ 2014ADIPSGDMGuidelinesV18.11.2014.pdf [accessed June 2015] 2014.

Negrato 2012
Negrato CA, Montenegro RM Jr, Von Kostrisch LM, Guedes MF, Mattar R, Gomes MB. Insulin analogues in the treatment of diabetes in pregnancy. *Arquivos Brasileiros de Endocrinologia e Metabologia* 2012;**56**(7):405–14.

NICE 2008
National Institute for Health and Clinical Excellence (NICE). *Diabetes in Pregnancy: Management of Diabetes and*

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

its Complications from Pre-conception to the Postnatal Period. NICE Clinical Guideline 63. London: NICE, 2008.

NICE 2015
National Institute for Health and Clinical Excellence (NICE). *Diabetes in Pregnancy: Management of Diabetes and its Complications from Pre-conception to the Postnatal Period. NICE Clinical Guideline NG3*. London: NICE, 2015.

Petry 2010
Petry CJ. Gestational diabetes: risk factors and recent advances in its genetics and treatment. *British Journal of Nutrition* 2010;**104**(6):775–87.

Pettitt 1985
Pettitt DJ, Bennett PH, Knowler WC, Baird HR, Aleck KA. Gestational diabetes mellitus and impaired glucose tolerance during pregnancy. Long-term effects on obesity and glucose tolerance in the offspring. *Diabetes* 1985;**34** (Suppl 2):119–22.

Pettitt 1993
Pettitt DJ, Nelson RG, Saad MF, Bennett PH, Knowler WC. Diabetes and obesity in the offspring of Pima Indian women with diabetes during pregnancy. *Diabetes Care* 1993;**16**(1):310–4.

Reece 2009
Reece EA, Leguizamon G, Wiznitzer A. Gestational diabetes: the need for a common ground. *Lancet* 2009;**373** (9677):1789–97.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Shah 2008
Shah BR, Retnakaran R, Booth GL. Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. *Diabetes Care* 2008;**31**(8):1668–9.

Solomon 1997
Solomon CG, Willett WC, Carey VJ, Rich-Edwards J, Hunter DJ, Colditz GA, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. *JAMA* 1997;**278**(13):1078–83.

Suman Rao 2013
Suman Rao PN, Shashidhar A, Ashok C. *In utero* fuel homeostasis: Lessons for a clinician. *Indian Journal of Endocrinology and Metabolism* 2013;**17**(1):60–8.

Tran 2013
Tran TS, Hirst JE, Do MA, Morris JM, Jeffrey HE. Early prediction of gestational diabetes mellitus in Vietnam: clinical impact of currently recommended diagnostic criteria. *Diabetes Care* 2013;**36**(3):618–24.

Vohr 2008
Vohr BR, Boney CM. Gestational diabetes: the forerunner for the development of maternal and childhood obesity and metabolic syndrome?. *Journal of Maternal-Fetal Medicine* 2008;**21**(3):149–57.

Whincup 2008
Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, et al. Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 2008;**300**(24):2886–97.

WHO 1999
World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Report of a WHO Consultation. Part 1*. Geneva, Switzerland: WHO, 1999.

WHO 2014
World Health Organization. *WHO Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy*. Report WHO/NMH/MND/13.2. Geneva, Switzerland: WHO, 2014.

Zhang 2006
Zhang C, Liu S, Solomon CG, Hu FB. Dietary fiber intake, dietary glycemic load, and the risk for gestational diabetes mellitus. *Diabetes Care* 2006;**29**(10):2223–30.

References to other published versions of this review

Alwan 2009
Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD003395.pub2]

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Examples of diagnostic criteria for gestational diabetes mellitus

Organisation/ professional body	Screening criteria	Diagnostic criteria				
	One-hour oral glucose challenge test	Oral glucose tolerance test	Fasting	One hour	Two hour	Three hour

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

ADA 2015b* , IADPSG 2010*, ADIPS 2014* (Nankervis 2014) ; WHO 2014*	-	75 g	≥ 5.1 mmol/L (≥ 92 mg/dL)	≥ 10 mmol/L (≥ 180 mg/dL)	≥ 8.5 mmol/L (≥ 153 mg/dL)	-
ADA 2015b	50 g (≥ 7.8 mmol/L; ≥ 140 mg/dL)	75 g	≥ 5.1 mmol/L (≥ 92 mg/dL)	≥ 10 mmol/L (≥ 180 mg/dL)	≥ 8.5 mmol/L (≥ 153 mg/dL)	-
ACOG 2013 Carpenter and Coustan^ or National Diabetes Data Group^	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)
	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)
NICE 2008; WHO 1999*; ADIPS 1998 (Hoffman 1998)		75 g	≥ 7.0 mmol/L (≥ 126 mg/dL)	-	≥ 11.1 mmol/L (≥ 200 mg/dL)	-
NICE 2015	-	75 g	≥ 5.6 mmol/L (≥ 101 mg/dL)	-	≥7.8 mmol/L (140 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 (recommends either the one step or two step strategy)
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
mmol/L - millimoles per litre
mg/dL - milligramme per decilitre

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APPENDICES

Appendix 1. Trial registry search terms

gestational diabetes OR GDM
diabetes AND pregnancy

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

Luke Grzeskowiak: none known

Michelle Downie: has received honorarium for lectures (and partial sponsorship to attend conferences) from Novo Nordisk and Sanofi Aventis.

Caroline A Crowther: none known

Kathryn Williamson: has been awarded the Auckland Medical Research Foundation Ruth Spencer Fellowship in support of her doctoral studies at The University of Auckland.

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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

- National Institute for Health Research (NIHR), UK.

NIHR Cochrane Programme Grant Project: 13/89/05 - Pregnancy and childbirth systematic reviews to support clinical guidelines

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NOTES

The original review Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. Cochrane Database of Systematic Reviews 2009, Issue 3. Art. No.: CD003395. DOI: 10.1002/14651858.CD003395.pub2. 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;
- 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 methods template used by the Cochrane Pregnancy and Childbirth Review Group.

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