Lifestyle interventions for the treatment of women with gestational diabetes (Protocol)

Brown J, Alwan NA, West J, Brown S, McKinlay CJD, Farrar D, Crowther CA

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Lifestyle interventions 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 lifestyle interventions in treating women with gestational diabetes.

BACKGROUND

The original review on *Treatments for gestational diabetes* (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 (this review)

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

Insulin for the treatment of women with gestational diabetes

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; 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 and not identified through early (first trimester) pregnancy screening (HAPO 2008; IADPSG 2010; Metzger 1998; Nankervis 2014; WHO 2014). Women meeting diagnostic criteria for overt diabetes would not be considered to

have GDM, however until recently, confirmation of overt diabetes was only possible in the postpartum period. With the uptake of early screening in the first trimester with glycated or glycosylated haemoglobin - HbA1C (glycated or glycosylated haemoglobin is a form of haemoglobin measured primarily to identify the average plasma glucose concentration over a period of time), more women with overt diabetes will be diagnosed and treated appropriately (Ministry of Health 2014 - New Zealand).

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; Kleinwechter 2014; 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 2007; Mulla 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 (ADA 2013; IADPSG 2010; Nankervis 2014; NICE 2015; WHO 1999; WHO 2014). 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 that 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 GDM

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 an increased risk of fetal macrosomia (Langer 2005).

Risk factors associated with GDM

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 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/m²) or obesity (equal to or greater than 30 kg/m²) (Kim 2010a), and excessive weight gain during pregnancy, especially for those who are already overweight or obese (Hedderson 2010).

Clinical outcomes for women with pregnancy hyperglycaemia

Adverse outcomes have been consistently reported at higher rates in women diagnosed with GDM and their infants compared with 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 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), which increases the risk of birth injury, including shoulder dystocia, perinatal asphyxia, bone fractures and nerve palsies (Esakoff 2009; Henriksen 2008; Langer 2005; Metzger 2008). 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).

Babies born to women with GDM, compared with babies born to women without GDM, have significantly greater skinfold measures and fat mass (Catalano 2003), have greater adiposity (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. For longer-term outcomes there is some evidence to suggest a link between maternal gestational diabetes and developmental delay (Dione 2008) and increased risk of Attention Deficit Hyperacticivity Disorder (Nomura 2012).

Description of the intervention

GDM management aims to optimise glycaemic control and consequently improve pregnancy outcomes (Kim 2010b). Providing dietary and lifestyle advice is usually recommended as the primary therapeutic strategy for women with GDM (ACOG 2013; ADA 2015a; Hoffman 1998; NICE 2015). If diet and lifestyle management alone are insufficient to achieve targets for maternal glycaemic control, insulin therapy or oral anti-diabetic pharmacological therapies such as glibenclamide and metformin can be added (ACOG 2013; ADA 2013; Hoffman 1998; NICE 2015; Silva 2010; Simmons 2004). As part of GDM management, maternal glucose monitoring and ultrasonography are advised to monitor the effectiveness of treatment and to guide care for birth (ACOG 2013; Hoffman 1998; NICE 2015). However, treatment recommendations differ across countries, for example, serial ultrasonography is not recommended to guide treatment management in the New Zealand Ministry of Health guidelines (Ministry of Health 2014).

Dietary intervention for managing GDM

Diet therapy is the primary strategy for managing GDM. Elevated blood glucose concentrations, in particular elevations in post-prandial glucose are associated with adverse pregnancy outcomes in GDM (de Veciana 1995). The role of head-to-head dietary interventions for treatment of women with GDM has been described in the Cochrane systematic review by Han 2013 and will not be included in this systematic review.

Carbohydrate-containing foods are important sources of energy, vitamins, minerals and fibre and are the main nutrient affecting blood glucose concentrations (Reader 2007). Blood glucose concentrations are affected by both total amount and type of carbohydrates consumed (Reader 2007). Glycaemic index (GI) is a ranking of the effects of carbohydrates on blood glucose concentrations (Jenkins 1981). Foods with a low GI (less than 55) produce

a lower post-prandial glucose elevation and area under the glucose curve; foods with a high GI (more than 70) produce a rapid increase in post-prandial blood glucose concentrations (Jenkins 1981). Outside of pregnancy, consumption of low-GI diets by people with diabetes seems to help lower glycated or glycosylated haemoglobin - HbA1C (Thomas 2010). Use of low-GI diets in GDM management seems to be beneficial in reducing the need for insulin, though the evidence is limited (Moses 2009). Polyunsaturated fatty acids may be protective against impaired glucose tolerance, while saturated fatty acids can increase glucose and insulin concentrations in women with GDM (Ilic 1999). Reducing blood lipid concentrations may improve glycaemic control and pregnancy outcomes in GDM (Barrett 2014). However, the specific amount and sources of fat that are beneficial for GDM management are not clear (Kim 2010b). Therefore, recommendations on the fat intake for women with GDM have not yet been promulgated (ACOG 2013; Hoffman 1998; Metzger 2007; (New Zealand) Ministry of Health 2014; NICE 2015). Recommendations on the intake of other nutrients for women with GDM are usually based on the general recommendations for people with diabetes mellitus outside pregnancy (Cheung 2009).

Physical activity during pregnancy for managing GDM

The role of supplementary physical activity interventions with no additional physical activity for the management of glycaemic control in women with diabetes in pregnancy (including GDM) was one of the comparisons described in the Cochrane review by Ceysens 2006. In non-pregnant women with type 2 diabetes, physical activity (in addition to diet and insulin) helped to normalise blood glucose levels (Tuomilehto 2001). Caution is required when generalising this evidence to pregnant women but it potentially suggests that during pregnancy mild exercise could reduce the risk of complications related to high blood glucose and high insulin levels, including macrosomia, birth trauma, respiratory distress, neonatal hypoglycaemia and hypocalcaemia. Exercise interventions alone for treating women with gestational diabetes will not be included in this systematic review.

Appropriate weight gain during pregnancy

Interventions for preventing excessive weight gain in pregnancy (diet or exercise or both) have been described in the Cochrane systematic review by Muktabhant 2015, which included 65 randomised controlled trials of which seven recruited women who were at high risk of gestational diabetes. Given the high prevalence of overweight and obesity in women with GDM, dietary interventions for appropriate pregnancy weight gain are routinely included as a part of nutritional management of GDM (Kim 2010b). Small reductions in weight improve glycaemic control (ACOG 2005), but the implications in pregnancy for the mother and fetus are unclear.

In 2009, the American Institute of Medicine updated its' guidelines for weight gain during pregnancy. Guidance is stratified by pre-pregnancy BMI, i.e. women with a pre-pregnancy BMI between 25 and 29.9 kg/m² should aim for 6.8 to 11.4 kg weight gain and those with pre-pregnancy BMI of 30 kg/m² or more should aim for 5 to 9 kg weight gain (IOM 2009). However, the degree of energy restriction for pre-pregnancy overweight and obese women to achieve these weight gain goals is unknown and is based on observational data (Kim 2010b).

Dietary interventions provided for women with GDM should ensure adequate nutrients for normal fetal growth and maternal health, but not induce weight loss or excessive weight gain during pregnancy; the main aim however is to promote optimal glycaemic control (ACOG 2013; Hoffman 1998; Metzger 2007; NICE 2015).

Combined dietary intervention and physical activity during pregnancy for managing GDM

Some interventions may involve a combination of dietary and physical activity modalities. Regular physical activity may help normalise maternal blood glucose for pregnant women with gestational diabetes and in combination with dietary interventions may reduce the need for oral anti-diabetic agents or insulin. As women with gestational diabetes are at increased risk of developing type 2 diabetes in the future, regular physical activity may also help reduce the risk of this long-term complication (Tuomilehto 2011).

Other interventions during pregnancy for managing GDM

There may be other interventions, including psychological approaches that may be used independently or alongside physical activity or dietary modalities such as mindfulness eating, yoga or spiritual support.

How the intervention might work

Role of diet

A carbohydrate-controlled diet (with carbohydrates distributed evenly throughout the day) that provides adequate nutrition, alongside glycaemic control and avoids ketonuria (ketones are produced when stored fat is utilised to produce energy in the absence of glucose) is thought to be optimal to reduce complications associated with gestational diabetes (Dornhorst 2002). Other elements of diet such as fat and fibre are also thought to influence maternal blood glucose concentrations (Zhang 2006). Excess fetal growth is most effectively limited by low post-prandial maternal glucose levels (de Veciana 1995; Dornhorst 2002; Harmon 2011; Rowan

2011; Weisz 2005). Dietary advice in the second trimester, as insulin resistance is developing may help reduce the risk of adverse outcomes associated with GDM (Dornhorst 2002).

Role of physical activity

Insulin sensitivity in skeletal muscle is related to the degree of physical activity, and therefore, physical activity interventions may improve insulin sensitivity and glucose control in individuals with diabetes (Asano 2014).

Glucose enters skeletal muscle cells via facilitated diffusion through a glucose transporter (GLUT4). Peripheral clearance of glucose in skeletal muscle depends on blood flow to muscle, expression of GLUT4 transporters and intracellular utilisation of glucose through glycolysis and glycogenesis. Translocation of the GLUT4 transporter is induced by insulin and insulin-independent mechanisms (Richter 2001). Exercise increases glucose uptake in skeletal muscle (Asano 2014), and improves glucose homeostasis and insulin sensitivity in skeletal muscle. Exercise potentiates most of the insulin-mediated post-receptor events that lead to an increased expression of GLUT4, and GLUT4 translocation from intracellular stores to the muscle membrane. These exercise-induced improvements in glucose uptake, however, are not limited to changes in GLUT4 expression. The improvements in insulin sensitivity after regular exercise may be related to changes in expression and/or activity of proteins involved in insulin signal transduction in skeletal muscle. As such, the enhanced glucose uptake in skeletal muscle attributed to exercise might be related to an increased expression and activity of key proteins for insulin signalling such as insulin receptor, insulin receptor substrate, and phosphatidylinositol 3-kinase (Chibalin 2000; Dela 1993; Hjeltnes 1998). Physical activity improves blood supply to the active skeletal muscles (Jensen 2004), counteracts the ability of lipids to induce insulin resistance (Schenk 2005), and modifies the hormonal regulation of hepatic glucose output. These exercise-induced alterations in muscle glucose handling explain most of the insulin-sensitising and diabetes-preventing effects of exercise, and partly explain why the many defects of insulin action observed in type 2 diabetes and insulin resistance are reversed by the effects of exercise (Zierath 2002).

Self-monitoring of blood glucose

Self-monitoring of blood glucose is performed by most women with GDM. Evidence has suggested that self-monitoring between four and seven times per day (including fasting and post-prandial measurements) can contribute to improved maternal and perinatal outcomes (ADA 2001) and is likely to be most effective when combined with effective treatment.

Why it is important to do this review

GDM affects a significant proportion of pregnant women and the prevalence is increasing worldwide (Bottalico 2007; Dabelea 2005; Mulla 2010). GDM is associated with an increased risk of a range of adverse pregnancy outcomes and these adverse health outcomes repeat across generations (Metzger 2008; Mulla 2010), which has important implications for the future. Providing dietary and lifestyle advice is usually recommended as the primary therapeutic strategy for women with GDM (ACOG 2013; Hoffman 1998; (New Zealand) Ministry of Health 2014; NICE 2015).

'*Different types of dietary advice for women with gestational diabetes mellitus*' (Han 2013). This review examined the effects of two or more forms of the same type of dietary interventions compared with each other for treating women with GDM, i.e. standard dietary advice compared with individualised dietary advice, individual dietary education sessions compared with group dietary education sessions, single dietary counselling session compared with multiple dietary counselling sessions.

'*Exercise for diabetic pregnant women*' (Ceysens 2006). This review evaluated the effects of physical activity interventions +/- dietary interventions compared with no additional physical activity intervention for women with diabetes in pregnancy and the trials included in the review recruited women with gestational diabetes.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We will include published or unpublished randomised controlled trials or cluster-randomised trials in full text or abstract format. Quasi-randomised and cross-over trials will be excluded. Conference abstracts will be handled in the same way as full-text publications.

Types of participants

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

Types of interventions

We will include randomised trials comparing lifestyle interventions (as defined by trialists) with:

- expectant management, standard care;
- other lifestyle intervention or combination of lifestyle interventions not described above.

The aim of the interventions will be to maintain maternal glycaemic targets during pregnancy in women with gestational diabetes.

Lifestyle interventions should include a combination of at least two or more of the following interventions:

- diet;
- physical activity;
- education;
- behavioural change;
- regimens of self-monitoring of blood glucose;
- other intervention not previously specified.

These interventions may or may not require adjunctive pharmacotherapy (oral anti-diabetic pharmacological therapies, insulin) used to treat women with gestational diabetes.

Interventions examining the comparison of different dietary interventions or the effects of exercise alone will not be included in this review as they are already included in other Cochrane systematic reviews (Han 2013 and Ceysens 2006 respectively).

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 (SGA) age (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
- 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 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 randomised 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. Where cluster-randomised trials are included we will refer to the *Handbook* sections 16.3.2 and 16.4.3 for assessing bias.

(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.

(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/child/adult 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 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 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 or Hoffman 1998 versus New Zealand Ministry of Health 2014 versus other not previously specified

- Timing of diagnosis: early (< 28 weeks' gestation) versus late ($\geq$ 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 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, and conference abstracts will be excluded from the meta-analysis.
We will also investigate the effect of the randomisation unit (i.e. where we include cluster-randomised trials along with individually-randomised trials).

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* *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
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^ 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)	-

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

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

APPENDICES

Appendix 1. Clinical trial registry search strategy

gestational diabetes OR GDM
diabetes AND pregnancy

CONTRIBUTIONS OF AUTHORS

Julie Brown guarantees this review.

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

DECLARATIONS OF INTEREST

Julie Brown: none known

Nisreen A Alwan: none known

Jane West: none known

Stephen Brown: none known

Christopher JD McKinlay: none known

Diane Farrar: none known

Caroline A Crowther is the lead investigator for the ACHOIS trial that assessed treatment for women with mild gestational diabetes. This will be considered for inclusion in this review. However, Professor Crowther will not be involved in the decisions about inclusion of data or any data extraction from that trial.

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Internal sources

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- Liggins Institute, New Zealand.

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External sources

- Australian Satellite of the Cochrane Pregnancy and Childbirth Review Group, Australia.

Support for infrastructure from the Australian Satellite of the Cochrane Pregnancy and Childbirth Review Group

- National Institute for Health Research (NIHR), UKNIHR Cochrane Programme Grant Project: 13/89/05 - Pregnancy and childbirth systematic reviews to support clinical guidelines, UK.

NOTES

The original review (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 (this review)

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

Insulin for the treatment of women with gestational diabetes

There will be similarities in the background, methods and outcomes between these three systematic reviews.