Different intensities of glycaemic control for women with gestational diabetes mellitus (Protocol)

Crawford TJ, Brown J, Alsweiler J, Martis R, Crowther CA

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[Intervention Protocol]

Different intensities of glycaemic control for women with gestational diabetes mellitus

Tineke J Crawford[1], Julie Brown[1], Jane Alsweiler[2], Ruth Martis[1], Caroline A Crowther[1,3]

[1]Liggins Institute, The University of Auckland, Auckland, New Zealand. [2]Neonatal Intensive Care Unit, Auckland Hospital, Auckland, New Zealand. [3]ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia

Contact address: Julie Brown, Liggins Institute, The University of Auckland, 85 Park Road, Grafton, Auckland, 1023, New Zealand. j.brown@auckland.ac.nz.

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ABSTRACT

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

To assess the effect of different intensities of glycaemic control in pregnant women with gestational diabetes for improving maternal and infant outcomes.

BACKGROUND

Description of the condition

Gestational diabetes mellitus is glucose intolerance, of varying levels of severity, that first occurs, or is first identified in pregnancy (Alberti 1998). This widely accepted definition also includes a small proportion of women (< 3%) who may have undiagnosed pre-existing type 1 or type 2 diabetes first detected during screening in pregnancy, as well as those women whose glucose intolerance is solely related to pregnancy (Nankervis 2013). The global prevalence is reported to be between 1% to 24.3% of pregnancies affected, depending on the diagnostic criteria used and the ethnicity (ACOG 2013; Bottalico 2007; Ferrara 2007; NICE 2008), and is likely to increase with the reported global obesity epidemic (Zhang 2010). Obesity has been identified as a significant risk factor for gestational diabetes (Boney 2005; Mokdad 2003; Rosenberg 2005).

During pregnancy, hormones released by the placenta cause an increase in maternal insulin resistance to ensure a constant supply of glucose and other nutrients to the growing fetus (McCance 2011). The maternal pancreas compensates for the pregnancy-induced insulin resistance by secreting more insulin. Gestational diabetes occurs when this compensatory mechanism fails and not enough insulin is available to metabolise glucose (McCurdy 2010). The maternal blood glucose concentration then increases resulting in hyperglycaemia. Increased amounts of glucose cross the placenta, over-nourishing the fetus, with increased fetal insulin secretion in response (Evans 2009). Increased fetal insulin may act as a growth stimulating factor (Pedersen 1954).

Recognised risk factors for developing gestational diabetes include obesity, advanced maternal age, weight gain in pregnancy, and a family history of type 2 diabetes (Zhang 2010). In addition, cer-

tain ethnicities, such as Asian, African American, Native American, Hispanic, and Pacific Island women have an increased risk (Schneider 2012).

Gestational diabetes has major short- and long-term implications for both the mother and her baby. Women with gestational diabetes are at higher risk of developing gestational hypertension and pre-eclampsia, and are at increased risk of having a caesarean section (McCance 2011). In the long-term, these women are at significantly increased risk of developing cardiovascular disease and over half will develop type 2 diabetes within five to 10 years (Bellamy 2009). The infants of women with gestational diabetes have a greater incidence of being born large-for-gestational age and macrosomic (variously defined as birthweight greater than 4000 g to 4500 g) (Young 2013), which increases the risk of shoulder dystocia and associated birth trauma such as bone fractures and nerve palsy (Athukorala 2006). Macrosomia has been associated with developmental delay in childhood (Ornoy 2005; Slining 2010). In the neonatal period, these infants are at higher risk of hypoglycaemia as they adjust to not having the high maternal glucose supply (Devlieger 2008). Neonatal hypoglycaemia is associated with developmental delay in childhood (Lucas 1988). A risk of major fetal congenital malformations and an increased risk of stillbirth and perinatal mortality have also been reported in the literature (Balsells 2009; Landon 2009; McCance 2011). There are life-long health risks to the infants of mothers with gestational diabetes such as higher rates of obesity and type 2 diabetes in childhood (Simmons 2010), and an increased risk of diabetes, hypertension, and cardiovascular disease in later life (Ornoy 2011).

Screening and diagnosis of gestational diabetes remain controversial topics, with some countries recommending universal screening of all pregnant women between 24 to 28 weeks' gestation (Nankervis 2013), and others only recommending selective screening (NICE 2008). The amount of glucose recommended for the diagnostic oral glucose tolerance test differs between countries (75 g and 100 g) and there is significant variation in the fasting, one, two and three hour postprandial plasma glucose concentrations above which gestational diabetes is diagnosed (ACOG 2013; Nankervis 2013; NICE 2008; Thompson 2013; WHO 2013;). Similarly, there is wide variation internationally in treatment targets recommended for optimal outcomes (see Table 1). As evidence emerges that current target thresholds may need to be lower than previously thought to reduce morbidity (Hernandez 2011; Metzger 2008), professional organisations are increasingly advocating tighter treatment targets that are closer to observed blood glucose concentrations in pregnant women without gestational diabetes mellitus (HSE 2010; Nankervis 2013). However, concerns have been raised that tighter glycaemic targets may be associated with an increased risk of infants being born small-for-gestational age (Garner 1997; Langer 1989; Langer 1994), and a potential increased risk of hypoglycaemia in the mother (DCCT 1996), and therefore in, the fetus.

Description of the intervention

Treatment of gestational diabetes aims to reduce the risks of gestational diabetes for the mother and baby by controlling the high maternal blood glucose concentrations (Alwan 2009). Glucose control is usually measured by monitoring capillary blood glucose concentrations to ensure blood glucose concentrations are maintained within a pre-defined threshold (Metzger 2008). This may be achieved through the use of diet and lifestyle modifications (ADA 2001; Ministry of Health 2014; NICE 2008), or with the addition, if necessary, of pharmacological interventions such as oral hypoglycaemic medications or subcutaneous insulin (ACOG 2013; Ministry of Health 2014; NICE 2008). Trials of interventions for gestational diabetes usually compare different treatment strategies with glycaemic control as an outcome, not an intervention (Middleton 2012). The focus of this review is comparing different treatment targets of glycaemic control in women with gestational diabetes mellitus and the impact on maternal and fetal health.

How the intervention might work

There is a continuous relationship between increasing maternal blood glucose concentrations and detrimental maternal and fetal outcomes (Langer 1994; Metzger 2008). Treatment of gestational diabetes to maintain maternal blood glucose concentrations within certain target thresholds, reducing the physiological response of the fetus to elevated maternal blood glucose concentrations, has been shown to be beneficial in reducing perinatal morbidity (Crowther 2005; Landon 2009). The Maternal-Fetal Medicine Units Network (MFMU) trial (Landon 2009) and the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial (Crowther 2005) both compared treatment of gestational diabetes mellitus with no treatment. The MFMU Network trial had tighter glycaemic control targets (fasting plasma glucose < 5.3 mmol/L and two-hour postprandial < 6.7 mmol/L) than the ACHOIS trial (fasting plasma glucose < 5.5 mmol/L and two-hour postprandial < 7.0 mmol/L), and demonstrated a reduction in the risk of caesarean section (risk ratio (RR) 0.79, 97% confidence interval (CI) 0.64 to 0.99) not shown in the ACHOIS trial (RR 0.97, 95% CI 0.81 to 1.16), although both trials demonstrated reductions in birthweight and large-for-gestational age infants in women with gestational diabetes mellitus who received treatment compared with women who were not treated (Crowther 2005; Landon 2009). Such evidence suggests tighter glycaemic targets may be of benefit.

Why it is important to do this review

The evidence for optimal glycaemic targets for women with gestational diabetes is limited and of varying quality. It appears that women who have better controlled blood glucose concentrations

in pregnancy have a lower incidence of pre-eclampsia and large-for-gestational-age babies. The infants of these women have a reduced incidence of neonatal hypoglycaemia and perinatal mortality (Ministry of Health 2014). Target recommendations from international professional organisations for maternal glycaemic control vary widely, all relying on consensus as there is a lack of high quality evidence (ADA 2013; Metzger 2007; Nankervis 2013; NICE 2008; SIGN 2010)

In assessing evidence related to determining the optimal degree of glycaemic targets, this review will contribute to knowledge that can be used to minimise the risk of adverse birth outcomes and diabetic complications for pregnant women and their babies.

OBJECTIVES

To assess the effect of different intensities of glycaemic control in pregnant women with gestational diabetes for improving maternal and infant outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, cluster-randomised and quasi-randomised controlled trials, including abstracts, will be eligible for inclusion (Higgins 2011). Cross-over trials will not be eligible for inclusion.

Types of participants

Pregnant women diagnosed with gestational diabetes. Due to varying diagnostic methods and criteria, screening and subsequent diagnosis and diagnostic criteria, will be defined by individual trials. Women with known pre-existing type 1 or type 2 diabetes will be excluded.

Types of interventions

Trials that compare different intensities of glycaemic control, with pre-specified descriptions of intensity of control. Trials that use different target thresholds will be included. If a trial uses blood glucose concentrations as the measure of glycaemic control, where applicable, we will use the definitions of 'loose', 'moderate', 'tight' and 'very tight' used in the individual trials.

Types of outcome measures

Primary outcomes

Maternal

- Caesarean section.
- Pre-eclampsia.

Infant

- Perinatal (fetal and neonatal) mortality.
- Large-for-gestational age (birthweight greater than the 90^{th} centile; or as defined by individual trial).

Secondary outcomes

Maternal

- Maternal mortality.
- Weight gain during pregnancy.
- Placental abruption.
- Induction of labour.
- Mode of birth (normal vaginal birth, operative vaginal birth, caesarean section).
- Perineal trauma.
- Postpartum haemorrhage.
- Postpartum infection requiring use of antibiotics (variously defined).
- Hyperglycaemia requiring changes in management during pregnancy.
- Hypoglycaemia requiring treatment during pregnancy.
- Diabetic ketoacidosis.
- Glycaemic control achieved (e.g. blood glucose or HbA1c concentrations) (proportion of blood glucose concentrations within target).
- Use of pharmacological treatment (insulin, oral hypoglycaemics).
- Postnatal depression.
- Anxiety.
- Breastfeeding.
- Satisfaction with treatment/management.
- Adherence with treatment/management.

Long-term maternal outcomes

- Postnatal weight retention.
- Body mass index postnatally.
- Postnatal glucose tolerance.
- Development of type 2 diabetes mellitus.

- Hypertension.
- Blood lipids.

Infant

- Stillbirth.
- Neonatal death.
- Death in infancy or childhood.
- Death or severe morbidity (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy).
- Congenital fetal anomaly.
- Macrosomia (birthweight $\geq$ 4000 g, or as defined by individual trial).
- Small-for-gestational age (birthweight less than the 10^{th} centile, or as defined by individual trial).
- Shoulder dystocia.
- Bone fracture.
- Nerve palsy.
- Preterm birth.
- Gestational age at birth.
- Birthweight.
- Head circumference.
- Length.
- Z scores of birthweight, head circumference, length.
- Neonatal hypoglycaemia.
- Neonatal infection.
- Neonatal hyperglycaemia.
- Respiratory distress syndrome.
- Neonatal jaundice (hyperbilirubinaemia).
- Hypocalcaemia.
- Fetal adiposity (variously defined by trials, e.g. skin folds, fat mass).
- Ponderal index.

Childhood

- Appropriate weight for age.
- Anthropometry (weight, height, head circumference, adiposity, skinfold thickness, fat mass).
- Developmental delay (variously defined by individual trials).
- Neurosensory disability (variously defined by individual trials).

Adulthood outcomes

- Glucose tolerance/type 2 diabetes mellitus.
- Blood pressure.
- Blood lipids.
- Metabolic syndrome.

Health Services

- Additional requirements for families (such as change of diet, exercise, extra antenatal visits, glucose monitoring and strips).
- Use of healthcare services in pregnancy (consultations, blood glucose monitoring, length and number of antenatal visits, and to whom - midwife/obstetrician/physician).
- Admission to neonatal intensive care unit/nursery.
- Length of stay in neonatal intensive care unit/nursery.
- Maternal antenatal admission.
- Length of maternal postnatal stay.
- Cost of maternal care.
- Cost of offspring care.

Search methods for identification of studies

The following methods section of this review 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 (see Appendix 1 for search terms we plan to use).

Searching other resources

We will conduct a handsearch of relevant conference abstracts and will list these in the review.
We will not apply any language or date restrictions.

Data collection and analysis

The following methods section of this review 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 author.
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 author. 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 author. We will seek statistical advice for calculating intracluster correlations from cluster-randomised trials if identified.

(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.

The quality of the evidence will be assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons.

1. Pre-eclampsia.
2. Caesarean section.
3. Large-for-gestational age.
4. Perinatal mortality.
5. Neonatal hypoglycaemia.
6. Composite of death or severe morbidity (variously defined e.g. death, shoulder dystocia, bone fracture, nerve palsy).
7. Neurosensory disability.

The GRADE profiler (GRADEpro 2014) will be used 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 to the standard errors using the methods described in the *Handbook* [Section 16.3.6] using an estimate of the intracluster 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.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

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 T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity (Higgins 2011).

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.

We will not combine trials based on the individual trial definition of intensity of glycaemic control. We will use the mmol/L thresholds used in the trials and subgroup based on these if there is significant heterogeneity.

We plan to carry out the following subgroup analyses.

1. Types of strategies used to target or achieve glycaemic control, or both

i) diet and lifestyle changes alone

ii) oral hypoglycaemics +\- diet and lifestyle changes

iii) insulin therapy +\- diet and lifestyle changes

2. Criteria used for diagnosis of gestational diabetes

i) Canadian Diabetes Association (Thompson 2013)

ii) Australasian Diabetes in Pregnancy Society (Nankervis 2013)

iii) National Institute of Health and Clinical Excellence (NICE 2008)

iv) Any others identified by individual trial

3. Gestational age at diagnosis

i) < 24 weeks

ii) 24 to < 28 weeks

iii) ≥ 28 weeks

4. Primiparas versus multiparas.

5. Twin pregnancies versus singleton pregnancies.

The following outcomes will be used in subgroup analysis.

Maternal

- Caesarean section.
- Pre-eclampsia.

Infant

- Perinatal (fetal and neonatal) mortality.

- Large-for-gestational age (birthweight greater than the 90^{th} centile; or as defined by individual trial).

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of subgroup analyses quoting the Chi² statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

If cluster-randomised trials are identified for inclusion, we will carry out sensitivity analysis to investigate the effect of the randomisation unit. We will also carry out sensitivity analysis to explore the impact of including studies assessed as high risk of bias due to randomisation method (e.g. quasi-randomisation versus true randomisation), and allocation concealment on the primary outcomes. We will also perform sensitivity analysis by excluding trials assessed as high risk of bias due to missing data.

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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) and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Treatment targets for glycaemic control from Clinical Practice Guidelines

	Fasting plasma glucose (mmol/L)	1 hour postprandial (mmol/L)	2 hours postprandial (mmol/L)
Australasian Diabetes in Pregnancy Society Nankervis 2013	≤ 5.0	≤ 7.4	≤ 6.7
Canadian Diabetes Association Thompson 2013	3.8 to 5.2	5.5 to 7.7	5.0 to 6.6
National Institute of Health and Clinical Excellence NICE 2008	3.5 to 5.9	< 7.8	-
American Diabetes Association ADA 2013	≤ 5.3	≤ 7.8 OR	≤ 6.7

Table 1. Treatment targets for glycaemic control from Clinical Practice Guidelines (*Continued*)

5th International Workshop Metzger 2007	5.0 to 5.5	< 7.8	< 6.7 to 7.1

APPENDICES

Appendix 1. Search terms

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP).
glycemic control AND pregnancy
glycemic control AND pregnant
glycaemic control AND pregnancy
glycaemic control AND pregnant
glycaemic control AND gestational
glycemic control AND gestational
gestational diabetes mellitus AND treatment thresholds
gestational diabetes mellitus AND treatment targets

CONTRIBUTIONS OF AUTHORS

Tineke Crawford (TC) and Julie Brown (JB) were both involved in conceiving the review. TC was responsible for preparing the initial draft of the protocol, and designing the search strategies. JB and Caroline Crowther assisted in the preparation of the protocol. Jane Alsweiler and Ruth Martis provided additional comments and feedback.

DECLARATIONS OF INTEREST

Caroline Crowther, Julie Brown and Jane Alsweiler are principal investigators, and Ruth Martis is a doctoral student on the TARGET randomised controlled trial examining optimal glycaemic targets for gestational diabetes. None of the authors associated with the TARGET randomised controlled trial will be involved in data extraction or assessment of risk of bias. Tineke Crawford will lead the data extraction for TARGET and we will seek assistance from another researcher not associated with the trial.

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