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Dietary supplementation with myo-inositol in women during pregnancy for treating gestational diabetes (Protocol)

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[Intervention Protocol]

Dietary supplementation with myo-inositol in women during pregnancy for treating gestational diabetes

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

[1]Liggins Institute, The University of Auckland, Auckland, New Zealand. [2]ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. [3]Department of Paediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand

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 if dietary supplementation with myo-inositol during pregnancy is safe and effective, for the mother and fetus, in treating gestational diabetes.

BACKGROUND

Description of the condition

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (Alberti 1998). During pregnancy, the placenta releases hormones that increase maternal insulin resistance to ensure a consistent supply of glucose to the growing fetus (McCance 2011). In compensation for this, the maternal pancreas secretes more insulin to maintain glycaemic control. Gestational diabetes occurs when this compensatory mechanism malfunctions and there is not enough insulin for appropriate glucose metabolism (McCurdy 2010). This results in increased maternal blood glucose concentrations, or hyperglycaemia, and an increased amount of glucose crossing the placenta over-nourishing the fetus (McCurdy 2010).

The diagnosis of GDM is usually made using an oral glucose tolerance test (OGTT) between 24 to 28 weeks' gestation. The diagnostic criteria vary from country to country (ACOG 2013; ADA 2013; CDA 2008; IADPSG 2010; Nankervis 2013; NICE 2015; New Zealand Ministry of Health 2014) (Table 1), making overall estimates of prevalence difficult, but GDM is thought to affect between 1% and 24% of pregnancies (Ferrara 2007). GDM can have significant adverse effects on the immediate and long-term health of the mother and baby (The HAPO Study Cooperative Research Group 2008; Wang 2013; Wendland 2012) and the rising global incidence of GDM is exposing more women and infants to the increased risk of these short- and long-term health complications (Ferrara 2007).

Women with GDM are at greater risk of developing pre-eclampsia and undergoing a caesarean section (Alwan 2009), while long term, over half will go on to develop type 2 diabetes within 10

years (Kim 2002). Infants of mothers with GDM can grow disproportionately large for their gestational age (Catalano 2003). This in turn increases the likelihood of traumatic birth or shoulder dystocia (when the shoulders become stuck in the birth canal) leading to birth injuries such as bone fracture or nerve palsy (Crowther 2005; Landon 2009). Additional risks for the immediate health of the infant include respiratory distress syndrome, jaundice, hypoglycaemia, and admission to the neonatal intensive care unit (Crowther 2005; Landon 2009). In the long term, babies born to mothers with GDM have a high likelihood of being obese as children and adults, and are at increased risk of metabolic syndrome and subsequently developing diabetes, perpetuating the cycle of poor health outcomes (Boney 2005; West 2011). Identification of effective treatment measures for GDM is of great importance.

Description of the intervention

Both non-pharmacological and pharmacological interventions are used to treat gestational diabetes. Currently, dietary and lifestyle counselling is the first line of treatment for women with GDM. Oral hypoglycaemics and/or insulin therapy are recommended for women with GDM who are unable to maintain glycaemic control with dietary and lifestyle interventions alone (Metzger 1998; NICE 2015; New Zealand Ministry of Health 2014).

Myo-inositol has been identified as a potentially new and novel treatment for GDM (Croze 2013). Myo-inositol is one of the nine isomers (forms) of inositol, a simple carbohydrate and nutrient the body requires for many cell functions (Croze 2013). Common dietary sources of inositol include fresh fruit and vegetables, cereals, legumes and nuts (Clements 1980). Myo-inositol is available as a dietary supplement, in water-soluble powder form or as capsules. Myo-inositol has been used therapeutically in a number of settings. In women with polycystic ovarian syndrome (PCOS), myo-inositol supplementation has been associated with an improvement in insulin sensitivity, and ovulatory function (Genazzani 2008; Minozzi 2008; Papaleo 2007). Myo-inositol has been found to assist the normal production of thyroid hormone in patients with autoimmune thyroiditis (chronic inflammation of the thyroid gland) (Nordio 2013), and is associated with successful treatment of premenstrual dysphoric disorder, a mood disorder disrupting the social and/or occupational life of affected women (Carlomagno 2011). Increased numbers and quality of oocytes (immature eggs within the ovary) in women undergoing in vitro fertilisation treatment for a previous history of infertility have also been reported following myo-inositol supplementation (Unfer 2011).

A retrospective review of 46 pregnant women treated with myo-inositol compared to 37 controls, described myo-inositol as safe during the pre-pregnancy and early pregnancy period, when used in insulin-resistant conditions, with no reported side effects (D'Anna 2012).

How the intervention might work

The way insulin functions within the body is complex and still not fully understood (Cohen 2006; Croze 2013). Insulin has been shown to use second messengers to help transmit signals from insulin to its target cells. Second messengers increase the speed and strength of insulins message within its target cells (Croze 2013). Myo-inositol has been identified as a second messenger of insulin improving the body's sensitivity to the effects of insulin (Larner 2010; Saltiel 1990).

Why it is important to do this review

A Cochrane systematic review has found some limited evidence to suggest that myo-inositol may be effective at preventing the onset of GDM (Crawford 2015). Given the beneficial effects observed on insulin sensitivity, myo-inositol may be useful as a treatment for women with gestational diabetes.

OBJECTIVES

To assess if dietary supplementation with myo-inositol during pregnancy is safe and effective, for the mother and fetus, in treating gestational diabetes.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials and cluster-randomised trials, including conference abstracts, assessing the effects of myo-inositol for the treatment of gestational diabetes mellitus (GDM). We will exclude quasi-randomised trials and cross-over trials.

Types of participants

Pregnant women with a diagnosis of GDM (as defined by trialists). Women with pre-existing type 1 or type 2 diabetes will be excluded.

Types of interventions

The intervention will include administration of any dose of myo-inositol, alone or in a combination preparation, after diagnosis of GDM in pregnancy, for the treatment of GDM. We will include

studies where the intervention is compared with those who received no treatment, placebo or another intervention.

Types of outcome measures

Primary outcomes

Maternal outcomes

1. Hypertensive disorders of pregnancy (including pre-eclampsia, eclampsia, pregnancy-induced hypertension)
2. Caesarean section
3. Development of subsequent type 2 diabetes mellitus (timeframe of long-term follow-up defined by trialists)

Neonatal outcomes

1. Large-for-gestational age (birthweight greater than the 90th centile; or as defined by individual trial)
2. Perinatal mortality (stillbirth and neonatal mortality)
3. Mortality or morbidity composite (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy)
4. Neurosensory disability

Secondary outcomes

Maternal outcomes

1. Induction of labour
2. Perineal trauma
3. Placental abruption
4. Postpartum haemorrhage
5. Postpartum infection
6. Weight gain during pregnancy
7. Adherence to the intervention (as defined by trialists)
8. Behaviour changes associated with the intervention (as defined by trialists)
9. Relevant biomarker changes associated with the intervention (e.g. adiponectin, free fatty acids, triglycerides, high-density lipoproteins, low-density lipoproteins, insulin)
10. Breastfeeding (e.g. at discharge, six weeks postpartum)
11. Use of additional pharmacotherapy
12. Glycaemic control during/end of treatment (as defined by trialists)
13. Maternal hypoglycaemia
14. Maternal mortality
15. Sense of well-being and quality of life
16. Views of the intervention

Long-term maternal outcomes

1. Postnatal depression
2. Postnatal weight retention or return to pre-pregnancy weight
3. Body mass index (BMI)
4. GDM in a subsequent pregnancy
5. Type 1 diabetes mellitus
6. Impaired glucose tolerance
7. Cardiovascular health (as defined by trialists, including blood pressure, hypertension, cardiovascular disease, metabolic syndrome)

Neonatal/Infant outcomes

1. Stillbirth
2. Neonatal mortality
3. Gestational age at birth
4. Preterm birth (less than 37 weeks' gestation and less than 32 weeks' gestation)
5. Apgar score (less than seven at five minutes)
6. Macrosomia
7. Small-for-gestational age
8. Birthweight and z-score
9. Head circumference and z-score
10. Length and z-score
11. Ponderal index
12. Adiposity (as defined by trialists)
13. Shoulder dystocia
14. Bone fracture
15. Nerve palsy
16. Respiratory distress syndrome
17. Hypoglycaemia (as defined by trialists)
18. Hyperbilirubinaemia
19. Neonatal hypocalcaemia
20. Polycythaemia (increase in the number of red blood cells)
21. Relevant biomarker changes associated with the intervention (e.g. cord C-peptide, cord insulin)

Later childhood outcomes

1. Weight and z-scores
2. Height and z-scores
3. Head circumference and z-scores
4. Adiposity (e.g. as measured by BMI, skinfold thickness)
5. Blood pressure
6. Type 1 diabetes mellitus
7. Type 2 diabetes mellitus
8. Impaired glucose tolerance
9. Dyslipidaemia or metabolic syndrome
10. Educational achievement

Adulthood outcomes

1. Weight
2. Height
3. Adiposity (e.g. as measured by BMI, skinfold thickness)
4. Cardiovascular health (as defined by trialists, including blood pressure, hypertension, cardiovascular disease, metabolic syndrome)
5. Type 1 diabetes mellitus
6. Type 2 diabetes mellitus
7. Impaired glucose tolerance
8. Dyslipidaemia or metabolic syndrome
9. Employment, education and social status/achievement

Health services cost

1. Number of hospital or health professional visits (e.g. midwife, obstetrician, physician, dietitian, diabetic nurse)
2. Number of antenatal visits or admissions
3. Length of antenatal stay
4. Neonatal intensive care unit admission
5. Length of postnatal stay (mother)
6. Length of postnatal stay (baby)
7. Costs to families associated with the management provided
8. Costs associated with the intervention (as defined by trialists)
9. Cost of maternal care
10. Cost of offspring care

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 the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator.
For full search methods used to populate the Pregnancy and Childbirth Group's 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 (see Appendix 1 for search terms).

Searching other resources

We will search reference lists of retrieved studies. We will not apply any language or date restrictions.

Data collection and analysis

Selection of studies

Two review authors will independently assessed for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion. 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 based on the Cochrane Pregnancy and Childbirth Group's data extraction form. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will enter data into Review Manager software (RevMan 2014) and check for accuracy. If 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 assessed 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 assessed blinding separately for different outcomes or classes of outcomes.
We will assess the 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.

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 covering both short- and long-term outcomes for the main comparisons.

Maternal

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

Offspring (infant, child, adult)

1. Large-for-gestational age
2. Perinatal mortality (stillbirth and neonatal mortality)
3. Composite of serious neonatal outcomes
4. Neonatal hypoglycaemia (variously defined)
5. Offspring adiposity (e.g. as measured by BMI, skinfold thickness)
6. Offspring diabetes
7. Neurosensory disability

Assessment of the quality of the evidence using the GRADE approach

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 with 95% confidence intervals 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; these will also be presented with 95% confidence intervals.

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] (Higgins 2011) 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.

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 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 are included 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 plan to carry out the following subgroup analyses.

1. Obese women versus non-obese women
2. Polycystic ovary syndrome (PCOS) women versus non-PCOS women
3. Myo-inositol alone versus as a co-intervention
4. Dosage (high versus low)
5. Type of preparation (e.g. powder versus gel capsules)
6. Study design (individually-randomised trials versus cluster-randomised trials) if cluster-randomised trials are identified.

The following primary outcomes will be used in subgroup analysis.

Maternal outcomes

1. Hypertensive disorders of pregnancy (e.g. pre-eclampsia, eclampsia, pregnancy-induced hypertension)
2. Caesarean section
3. Development of subsequent type 2 diabetes mellitus

Neonatal outcomes

1. Large-for-gestational age
2. Perinatal mortality (stillbirth and neonatal mortality)
3. Composite of serious neonatal outcomes
4. Neurosensory disability

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.

ACKNOWLEDGEMENTS

Portions of the methods section of this protocol are based on a standard template used by the Cochrane Pregnancy and Childbirth Review Group. Outcomes may be similar to other Cochrane reviews on treatment for gestational diabetes due to the attempt to have consistency across all protocols and reviews on this condition.

This protocol came about whilst work was being conducted on the Cochrane systematic review '*Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes*' (Crawford 2015). It was recognised that studies were excluded from that review on the basis that they used myo-inositol for the treatment of gestational diabetes mellitus, rather than for prevention. This accounts for the similarities between certain aspects of this protocol and the *'Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes*' review.

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

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Diagnostic criteria for GDM

Organisation	Testing schedule	Abnormal values required for diagnosis of GDM	Threshold equal to or greater than			
			Fasting	1 hour	2 hours	3 hours
Australasian Diabetes in Pregnancy Society (Nankervis 2013)	OGTT	1	5.1 mmol/L	10.0 mmol/L	8.5 mmol/L	-
American Diabetes Association (ADA 2013)	75 g OGTT	1	5.1 mmol/L	10.0 mmol/L	8.5 mmol/L	-
American College of Obstetricians and Gynecologists* (ACOG 2013)	Either Carpenter & Coustan 100 g OGTT	2	5.3 mmol/L	10.0 mmol/L	8.6 mmol/L	7.8 mmol/L
	or NDDG 100 g OGTT	2	5.8 mmol/L	10.6 mmol/L	9.2 mmol/L	8.0 mmol/L
International Association of Diabetes and Pregnancy Study Groups (IADPSG 2010)	75 g OGTT	1	5.1 mmol/L	10.0 mmol/L	8.5 mmol/L	-
World Health Organization (Alberti 1998) National Institute for Health and Care Excellence (NICE	75 g OGTT	1	7.0 mmol/L	-	11.1 mmol/L	-

Table 1. Diagnostic criteria for GDM (*Continued*)

2015)						
Canadian Diabetes Association (CDA 2008)	75 g OGTT	2	5.3 mmol/L	10.6 mmol/L	8.9 mmol/L	-
New Zealand Ministry of Health (New Zealand Ministry of Health 2014)	75 g OGTT	1	5.5 mmol/L	-	9.0 mmol/L	-

OGTT: oral glucose tolerance test
* American College of Obstetricians and Gynecologists stipulates that either the Carpenter and Coustan or the National Diabetes Data Group (NDDG) thresholds are appropriate to use.

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

gestational diabetes AND myoinositol
gestational diabetes AND myo-inositol
gestational diabetes AND inositol
gdm AND myoinositol
gdm AND myo-inositol
gdm AND inositol

CONTRIBUTIONS OF AUTHORS

Tineke Crawford is guarantor for this review. Julie Brown is the contact person for this review.

All authors (TC, JB, JA and CAC) contributed to the preparation of this protocol.

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Tineke J Crawford: none known

Caroline A Crowther: none known

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