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Myo-inositol for preventing gestational diabetes (Protocol)

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Myo-inositol for preventing 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 assess if supplements of myo-inositol are safe and effective, for the mother and fetus, in preventing 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 (Metzger 1998). This condition imposes several complications for affected women and their babies making it crucial for an early diagnosis and management.

Screening for GDM varies from country to country, with some countries selectively screening based on risk factors (NICE 2008), and other countries using universal screening of all pregnant women (Nankervis 2013). Screening is usually done using the oral glucose challenge test (OGCT) followed by an oral glucose tolerance test (OGTT) if the challenge test is failed, between 24 and 28 weeks of pregnancy. A number of risk factors are associated with developing gestational diabetes mellitus (Nankervis 2013):

- previous GDM;
- previously elevated blood glucose level;
- ethnicity: south and southeast Asian, Aboriginal, Pacific Islander, Maori, Middle Eastern, non-Caucasian African;
- age $\geq$ 40 years;
- family history of diabetes mellitus (first degree relative with diabetes mellitus or a sister with GDM);
- obesity, especially body mass index (BMI) greater than 35 kg/m^2;
- previous macrosomia (baby with birthweight greater than 4500 g or greater than 90th percentile);
- polycystic ovarian syndrome;
- medications: corticosteroids, antipsychotics;
- pregnancy weight gain.

Several studies have reported an increasing pattern in GDM prevalence (Ferrara 2007). As many as 50% of women with GDM will develop type 2 diabetes within five years of the index pregnancy (Kim 2002). Gestational diabetes mellitus also doubles the risk of serious injury at birth, triples the likelihood of caesarean delivery, and quadruples the incidence of newborn intensive care unit (NICU) admission (Moore 2014). Infants of women with GDM are at increased risk of developing obesity, impaired glucose toler-

ance, and diabetes as children or young adults (Pettitt 1983; Pettitt 1988; Silverman 1998).

Description of the intervention

Both non-pharmacological and pharmacological interventions have been used to try and prevent gestational diabetes.

A Cochrane review *'Dietary advice in pregnancy for preventing gestational diabetes mellitus'* (Tieu 2008) concluded that while a low glycaemic index (GI) diet was beneficial for some outcomes for the mother (lower maternal fasting glucose concentration) and child (reduction in large-for-gestational-age infants, lower ponderal index), the evidence is limited. Similarly, the review *'Exercise for pregnant women for preventing gestational diabetes mellitus'* concluded that there is limited evidence to currently support exercise during pregnancy for the prevention of glucose intolerance or GDM (Han 2012). Currently, a review is in progress to assess the effects of physical exercise in combination with dietary advice for pregnant women for preventing GDM, and associated adverse health consequences for the mother and her infant/child (Crane 2013). Metformin is an oral anti-diabetic drug in the biguanide class. Metformin is the first-line drug of choice for the treatment of type 2 diabetes. Metformin has been used to prevent GDM in high-risk pregnancies (women with polycystic ovary syndrome - PCOS) and yielded contrasting results (Glueck 2008; Nestler 1999).

Myo-inositol is a nutrient in the vitamin B complex and is a naturally occurring sugar found in the human body (NCI). It is an isomer of inositol, one of the intracellular mediators of the insulin signal and is correlated with insulin sensitivity in type 2 diabetes (Kennington 1990; Suzuki 1994). Inositol is commonly found in cereals, corn, legumes and meat.

Due to its role as a second messenger, myo-inositol has many benefits. When used as a co-treatment, it ensured euthyroidism (normal production of thyroid hormone) in subclinical hypothyroidism patients with autoimmune thyroiditis (Nordio 2013). Also, myo-inositol has proven to be efficacious in treating premenstrual dysphoric disorder (PMDD), a mood disorder disrupting the social and/or occupational life of affected women (Carlomagno 2011). PCOS, a medical condition characterised by insulin resistance has been successfully treated with myo-inositol and folic acid (Papaloe 2007). Inositol has been reported to improve insulin sensitivity and ovulatory function in young women affected by PCOS in the D-chiro-inositol isomer (Nestler 1999) or in the myo-inositol isomer (Genazzani 2008). Furthermore, myo-inositol has shown to improve hyperandrogenism in women with PCOS (Minozzi 2008) and pregnancy outcomes in infertile women with poor oocyte quality (Unfer 2011).

How the intervention might work

Given the above beneficial effects on improving insulin sensitivity, myo-inositol may be useful for women with gestational diabetes. In a small randomised controlled trial of myo-inositol in 69 women with gestational diabetes, markers of insulin resistance were improved in the study group (n = 24) compared to the control group (n = 45) (Corrado 2011). A retrospective review of 46 pregnant women treated with myo-inositol compared to 37 controls described it as safe during the pre-pregnancy and early pregnancy period when used in insulin-resistant conditions (D'Anna 2011). No women in either of these studies reported side effects of treatment.

Why it is important to do this review

GDM is an increasing problem worldwide. Identification of effective preventive measures for GDM is of great importance.

O B J E C T I V E S

To assess if supplements of myo-inositol are safe and effective, for the mother and fetus, in preventing gestational diabetes.

M E T H O D S

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials and cluster-randomised trials as well as conference abstracts assessing the effects of myo-inositol for the prevention of gestational diabetes mellitus (GDM) will be included. We will exclude quasi-randomised trials and cross-over trials.

Types of participants

Pregnant women who are at risk of GDM (as defined by trialists) will be included. Women with pre-existing type 1 or type 2 diabetes will be excluded.

Types of interventions

The intervention will include administration of any doses of myo-inositol in pregnancy. We will include studies where such intervention is compared with those who received no treatment, placebo or another intervention.

Types of outcome measures

Primary outcomes

Maternal outcomes

1. Incidence of GDM (diagnostic criteria as defined in individual trials)
2. Pre-eclampsia
3. Caesarean section

Neonatal outcomes

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

Secondary outcomes

Maternal outcomes

1. Postnatal weight retention
2. Body mass index (BMI)
3. Development of type 2 diabetes mellitus
4. Development of type 1 diabetes mellitus
5. Impaired glucose tolerance (as defined in individual trials)
6. Insulin sensitivity (as defined in individual trials)
7. Incidence of pregnancy hyperglycaemia not meeting GDM diagnostic criteria (diagnostic criteria as defined in individual trials)
8. Induction of labour
9. Mode of birth (caesarean section, vaginal birth)
10. Perineal trauma
11. Pre-eclampsia (as defined by individual trials)
12. Weight gain during pregnancy
13. Adiponectin levels
14. Gestational age at screening for GDM
15. Postpartum haemorrhage
16. Postpartum infection
17. Placental abruption
18. Polyhydramnios
19. Compliance with treatment
20. Breastfeeding at discharge, six weeks postpartum
21. Women's sense of well-being and quality of life (as defined in individual trials)
22. Women's view of intervention

Infant outcomes

1. Macrosomia (as defined in individual trials)
2. Birthweight and z-score
3. Head circumference and z-score
4. Length and z-score
5. Small-for-gestational age (as defined in individual trials)
6. Neonatal hypoglycaemia requiring treatment (as defined in individual trials)
7. Gestational age at birth
8. Preterm birth (less than 37 weeks' gestational age)
9. Shoulder dystocia
10. Bone fracture
11. Nerve palsy
12. Respiratory distress syndrome
13. Hyperbilirubinaemia requiring treatment (as defined in individual trials)
14. Apgar scores (less than seven at five minutes)
15. Ponderal index
16. Fetal adipocity (as defined in individual trials)
17. Neonatal glucose concentration
18. Infant mortality (fetal, neonatal, perinatal)

Childhood outcomes

1. Weight
2. Height
3. Head circumference
4. Body mass index
5. Adiposity (fat mass/fat free mass (variously measured))
6. Blood pressure
7. Impaired glucose tolerance (as defined in individual trials)
8. Development of type 1 diabetes mellitus
9. Development of type 2 diabetes mellitus
10. Insulin sensitivity
11. Dyslipidaemia or metabolic syndrome
12. Neurodisability
13. Educational achievement

Adulthood outcomes

1. Weight
2. Height
3. BMI
4. Adipocity (fat mass/fat-free mass (variously measured))
5. Blood pressure
6. Impaired glucose tolerance (as defined in individual trials)
7. Development of type 1 diabetes
8. Development of type 2 diabetes
9. Insulin sensitivity (as defined in individual trials)
10. Dyslipidaemia or metabolic syndrome
11. Educational achievement

Health services cost

1. Number of hospital visits or health professional visits (e.g. midwife, obstetrician, physician, dietitian)
2. Antenatal visits for mother
3. Direct costs to families in relation to the management provided
4. Length of postnatal stay (mother)
5. Admission to neonatal ward/ neonatal intensive care unit
6. Length of postnatal stay (baby)
7. Cost of maternal care
8. 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 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 plan to search ClinicalTrials.gov and WHO ICTRP for planned, ongoing or unpublished trials. The search terms we plan to use are given in Appendix 1.

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 assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.
We will create a Study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management

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

Assessment of risk of bias in included studies

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

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

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

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

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

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

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

- unclear risk of bias.

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

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

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

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

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

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

(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. Incidence of GDM (diagnostic criteria as defined in individual trials)
2. Pre-eclampsia
3. Mode of birth
4. Large-for-gestational age (birthweight greater than the 90th centile; or as defined by individual trial)
5. Perinatal mortality
6. Fetal adiposity
7. Impaired glucose tolerance as a child/adult

GRADE profiler (GRADE 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 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] 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 Tau², I² and Chi² statistics. We will regard heterogeneity as substantial if an I² is greater than 30% and either a Tau² is greater than zero, or there is a low P value (less than 0.10) in the Chi² 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 Tau² and I².

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. Polycystic ovary syndrome (PCOS) women versus non-PCOS women
2. Obese women versus non-obese women
3. Dosage - high versus low dose
4. Timing of myo-inositol - pre-pregnancy versus first trimester

The following outcomes will be used in subgroup analysis.

Maternal outcomes

1. Incidence of GDM (diagnostic criteria as dened in individual trials)
2. Mode of birth (normal vaginal birth, operative vaginal birth, caesarean section)

3. Pre-eclampsia

Neonatal outcomes

1. Large-for-gestational age
2. Perinatal mortality

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 I² 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.

REFERENCES

Additional references

Carlomagno 2011
Carlomagno G, Unfer V, Buffo S, D'Ambrosio F. Myo-inositol in the treatment of premenstrual dysphoric disorder. *Human Psychopharmacology: Clinical and Experimental* 2011;**26**(7):526–30.

Corrado 2011
Corrado F, D'Anna R, Di Vieste G, Giordano D, Pintaudi B, Santamaria A, et al.The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes. *Diabetic Medicine* 2011;**28**:972–5.

Crane 2013
Crane M, Bain E, Tieu J, Han S, Middleton P, Crowther CA. Diet and exercise interventions for preventing gestational diabetes mellitus. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: 10.1002/14651858.CD010443]

D'Anna 2011
D'Anna R, Di Bendetto V, Rizzo P, Raffone E, Interdanto ML, Corado F, et al.Myo-inositol may prevent gestational diabetes in PCOS women. *Gynecological Endocrinology* 2012;**28**(6):440–2.

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

Genazzani 2008
Genazzani AD, Lanzoni C, Ricchieri F, Jasonni VM. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovarian syndrome. *Gynecological Endocrinology* 2008;**24**:139–44.

Glueck 2008
Glueck CJ, Pranikoff J, Aregawi D, Wang P. Prevention of gestational diabetes by metformin plus diet in patients with polycystic ovarian syndrome. *Fertility and Sterility* 2008;**89**:625–34.

GRADE 2014
McMaster University. GRADEpro. [Computer program on www.gradepro.org]. 2014. McMaster University, 2014.

Han 2012

Han S, Crowther CA, Middleton P. Exercise for pregnant women for preventing gestational diabetes mellitus. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD009021.pub2]

Higgins 2011

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

Kennington 1990

Kennington AS, Hill CR, Craig J, Bogardus C, Raz I, Ortmeyer HK, et. al. Low urinary chiro-inositol excretion in non-insulin-dependent diabetes mellitus. *New England Journal of Medicine* 1990;**323**:373–8.

Kim 2002

Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 2002;**25**:1862–8.

Metzger 1998

Metzger BE, Coustan DR. Proceedings of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. *Diabetes Care* 1998;**21 (Suppl. 2)**: B1–B167.

Minozzi 2008

Minozzi M, D'Andrea G, Unfer V. Treatment of hirsutism with myo-inositol: a prospective clinical study. *Reproductive Biomedicine Online* 2008;**17**(4):579–82.

Moore 2014

Moore TR. Diabetes Mellitus and Pregnancy. http://emedicine.medscape.com/article/127547-overview [accessed 27 Jan 2014].

Nankervis 2013

Nankervis A, Conn J. Gestational diabetes mellitus-negotiating the confusion. *Australian Family Physician* 2013;**42**(8):528–31.

NCI

NCI Dictionary of Cancer Terms. http://www.cancer.gov/dictionary (accessed July 2014).

Nestler 1999

Nestler JE, Jakubowicz DJ, Reamer P, Gunn RD, Allan G. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. *New England Journal of Medicine* 1999;**340**:1314–20.

NICE 2008

National Institute for Health and Clinical Excellence. Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period.. *Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period*. Manchester: NICE, 2008.

Nordio 2013

Nordio M, Pajalich R. Combined treatment with Myo-inositol and selenium ensures euthyroidism in subclinical

hypothyroidism patients with autoimmune thyroiditis. *Journal of Thyroid Research* 2013;**Article ID 424163**:5 pages. [DOI: 10.1155/2013/424163]

Papaloe 2007

Papaloe E, Unfer V, Baillargeon JP, De Santis L, Fusi F, Brigante C, et al.Myoinositol in patients with polycystic ovarian syndrome: a novel method for ovulation induction. *Gynecological Endocrinology* 2007;**23**:700–3.

Pettitt 1983

Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *New England Journal of Medicine* 1983;**308**:242–5.

Pettitt 1988

Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM: role of intrauterine environment. *Diabetes* 1988;**37**:622–8.

RevMan 2014

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schunemann 2009

Schunemann HJ. GRADE: from grading the evidence to developing recommendations. A description of the system and a proposal regarding the transferability of the results of clinical research to clinical practice [GRADE: Von der Evidenz zur Empfehlung.Beschreibung des Systems und Losungsbeitrag zur Ubertragbarkeit von Studienergebnissen]. *Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen* 2009;**103**(6):391–400.

Silverman 1998

Silverman BL, Rizzo TA, Cho NH, Metzger BE. Long-term effects of the intrauterine environment: The Northwestern University Diabetes in Pregnancy Center. *Diabetes Care* 1998;**21 (Suppl. 2)**:B142–B149.

Suzuki 1994

Suzuki S, Kawasaki H, Satoh Y. Urinary chiro-inositol excretion is an index marker of insulin sensitivity in Japanese type 2 diabetes. *Diabetes Care* 1994;**17**:1465–8.

Tieu 2008

Tieu J, Crowther CA, Middleton P. Dietary advice in pregnancy for preventing gestational diabetes mellitus. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD006674.pub2]

Unfer 2011

Unfer V, Raffone E, Rizzo P, Buffo S. Effect of a supplementation with myo-inositol plus melatonin on oocyte quality in women who failed to conceive in previous in vitro fertilization cycles for poor oocyte quality: a prospective, longitudinal, cohort study. *Gynecological Endocrinology* 2011;**27**:857–61.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search terms

ClinicalTrials.gov and WHO ICTRP
gestational diabetes AND myoinositol

WHAT'S NEW

Date	Event	Description
4 February 2015	Amended	Corrected typographical error in Methods section.

CONTRIBUTIONS OF AUTHORS

Julie Brown, Tineke Crawford, Jane Asweiler and Caroline Crowther all contributed to the preparation of the protocol and Jane Asweiler provided the clinical perspective. All review authors commented and contributed to the preparation of the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.