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Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes (Review)

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[Intervention Review]

Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes

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ABSTRACT

Background

Gestational diabetes, glucose intolerance with onset or first recognition during pregnancy, is a rising problem worldwide. Both non-pharmacological and pharmacological approaches to the prevention of gestational diabetes have been, and continue to be explored. Myo-inositol, an isomer of inositol, is a naturally occurring sugar commonly found in cereals, corn, legumes and meat. It is one of the intracellular mediators of the insulin signal and correlated with insulin sensitivity in type 2 diabetes. The potential beneficial effect on improving insulin sensitivity suggests that myo-inositol may be useful for women in preventing gestational diabetes.

Objectives

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

Search methods

We searched the Pregnancy and Childbirth Group's Trials Register, ClinicalTrials.gov, WHO ICTRP (2 November 2015) and reference lists of retrieved studies.

Selection criteria

We sought published and unpublished randomised controlled trials, including conference abstracts, assessing the effects of myo-inositol for the prevention of gestational diabetes mellitus (GDM). Quasi-randomised and cross-over trials were not eligible for inclusion, but cluster designs were eligible. Participants in the trials were pregnant women. Women with pre-existing type 1 or type 2 diabetes were excluded. Trials that compared the administration of any dose of myo-inositol, alone or in a combination preparation were eligible for inclusion. Trials that used no treatment, placebo or another intervention as the comparator were eligible for inclusion.

Data collection and analysis

Two review authors independently assessed trials for inclusion, risk of bias and extracted the data. Data were checked for accuracy.

Main results

We included four randomised controlled trials (all conducted in Italy) reporting on 567 women who were less than 11 weeks' to 24 weeks' pregnant at the start of the trials. The trials had small sample sizes and one trial only reported an interim analysis. Two trials were open-label. The overall risk of bias was unclear.

For the mother, supplementation with myo-inositol was associated with a reduction in the incidence of **gestational diabetes** compared with control (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.29 to 0.64; three trials; n = 502 women). Using GRADE methods this evidence was assessed as *low* with downgrading due to unclear risk of bias for allocation concealment in two of the included trials and lack of generalisability of findings. For women who received myo-inositol supplementation, the incidence of GDM ranged from 8% to 18%; for women in the control group, the incidence of GDM was 28%, using International Association of Diabetes and Pregnancy Study Groups Consensus Panel 2010 criteria to diagnose GDM.

Two trials reported on **hypertensive disorders of pregnancy**, a primary maternal outcome of this review. There was no clear difference in risk of hypertensive disorders of pregnancy between the myo-inositol and control groups (average RR 0.43, 95% CI 0.02 to 8.41; two trials; n = 398 women; $Tau^2 = 3.23$; $I^2 = 69\%$). Using GRADE methods, this evidence was assessed as *very low*, with downgrading due to wide confidence intervals with very low event rates, a small sample size, and lack of blinding and unclear allocation concealment methods, and a lack of generalisability. For women who received myo-inositol the risk of hypertensive disorders of pregnancy ranged from 0% to 33%; for women in the control group the risk was 4%.

For the infant, none of the included trials reported on the primary neonatal outcomes of this systematic review (**large-for-gestational age**, **perinatal mortality**, **mortality or morbidity composite**).

In terms of this review's secondary outcomes, there was no clear difference in the risk of **caesarean section** between the myo-inositol and control groups (RR 0.95, 95% CI 0.76 to 1.19; two trials; n = 398 women). Using GRADE methods, this evidence was assessed as *low*, with downgrading due to unclear risk of bias in one trial and lack of generalisability. For women who received myo-inositol supplementation, the risk of having a caesarean section ranged from 34% to 54%; for women in the control group the was 45%. There were no **maternal adverse effects** of therapy in the two trials that reported on this outcome (the other two trials did not report this outcome).

Two trials found no clear difference in the risk of **macrosomia** between infants whose mothers received myo-inositol supplementation compared with controls (average RR 0.35, 95% CI 0.02 to 6.37; two trials; n = 398 infants;$Tau^2 = 3.33$; $I^2 = 73\%$). Similarly, there was no clear difference between groups in terms of **neonatal hypoglycaemia** (RR 0.36, 95% CI 0.01 to 8.66) or shoulder dystocia (average RR 2.33, 95% CI 0.12 to 44.30, $Tau^2 = 3.24$; $I^2 = 72\%$).

There was a lack of data available for a large number of maternal and neonatal secondary outcomes, and no data for any of the long-term childhood or adulthood outcomes, or for health service cost outcomes.

Authors' conclusions

Evidence from four trials of antenatal dietary supplementation with myo-inositol during pregnancy shows a potential benefit for reducing the incidence of gestational diabetes. No data were reported for any of this review's primary neonatal outcomes. There were very little outcome data for the majority of this review's secondary outcomes. There is no clear evidence of a difference for macrosomia when compared with control.

The current evidence is based on small trials that are not powered to detect differences in outcomes including perinatal mortality and serious infant morbidity. All of the included studies were conducted in Italy which raises concerns about the lack of generalisability of the evidence to other settings. There is evidence of inconsistency and indirectness and as a result, many of the judgements on the quality of the evidence were downgraded to *low* or *very low quality* (GRADEpro Guideline Development Tool).

Further trials for this promising antenatal intervention for preventing gestational diabetes are encouraged and should include pregnant women of different ethnicities and varying risk factors and use of myo-inositol (different doses, frequency and timing of administration) in comparison with placebo, diet and exercise or pharmacological interventions. Outcomes should include potential harms including adverse effects.

PLAIN LANGUAGE SUMMARY

Taking myo-inositol as a dietary supplement during pregnancy to prevent the development of gestational diabetes

What is the issue?

This review aimed to investigate if myo-inositol is an effective antenatal dietary supplement for preventing gestational diabetes in pregnant women. Women who develop gestational diabetes have a higher risk of experiencing complications during pregnancy and birth, as well as developing diabetes later on in life. The babies of mothers who have gestational diabetes can be larger than they should be potentially causing injuries to the babies at birth. These babies are at risk of diabetes even as young children or young adults.

Why is this important?

The number of women being diagnosed with gestational diabetes is increasing around the world so finding simple and cost-effective ways to prevent women developing gestational diabetes is important. Myo-inositol is a naturally occurring sugar found in cereals, corn, green vegetables and meat that has a role in the body's sensitivity to insulin.

What evidence did we find?

We searched for studies on 2 November 2015 and included four small randomised controlled trials involving a total of 567 women who were less than 11 weeks' to 24 weeks' pregnant at the start of the trials. The quality of the evidence was assessed as *low* or *very low* and the overall risk of bias was unclear.

Myo-inositol was associated with a reduction in the rate of gestational diabetes (*low quality evidence*), reducing the incidence from 28% in women who did not take the supplement, to between 8% and 18% in the women who took it. There was no difference between groups in terms of the number of women who had hypertensive disorders of pregnancy (including pre-eclampsia, eclampsia and abnormally high blood pressure during pregnancy) (*very low quality evidence*). The trials did not provide any information about the number of babies that died (either before being born or shortly afterwards) or babies that were large-for-gestational age. There were no maternal adverse effects of therapy in the two trials that reported on this outcome (the other two trials did not mention this).

This review did not find any impact on other outcomes such as the risk of having a caesarean section (*low quality evidence*), a large baby, obstructed labour when the baby's shoulder becomes stuck (shoulder dystocia) or a baby with low blood glucose levels. This may be due to the trials being too small to detect differences in these outcomes and the outcomes not being reported by all trials. All four trials were from Italy.

The included trials did not report on a large number of other mother and baby outcomes listed in this review and nor were there any data relating to longer-term outcomes for the mother or the infant, or the cost of health services.

What does this mean?

Myo-inositol as a dietary supplement during pregnancy shows promise in preventing gestational diabetes but there is not enough evidence at this stage to support its routine use. Further large, well-designed, randomised controlled trials are required to assess the effectiveness of myo-inositol in preventing gestational diabetes and improving other health outcomes for mothers and their babies.

Ideally, future studies should consider involving women from different ethnicities and with differing risk factors for gestational diabetes. It would be useful for future studies to consider the ways that myo-inositol can be used (different doses, frequency and when to take it) and compare the intervention with a placebo control, diet and exercise or pharmacological interventions. We recommend that future studies utilise the outcomes listed in this review and that potential harms, including adverse effects are included.

Summary of findings for the main comparison. Myo-inositol for preventing gestational diabetes maternal outcomes (maternal outcomes)

Antenatal supplementation with myo-inositol for preventing gestational diabetes

Patient or population: pregnant women (women with pre-existing type 1 or type 2 diabetes are NOT included)
Intervention: Myo-inositol

Setting: Italy
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Myo-inositol				
Gestational diabetes mellitus	Study population		RR 0.43 (0.29 to 0.64)	502 (3 RCTs)	⊕⊕⊝⊝ LOW [1 2]	GDM diagnosed using IADPSG 2010 criteria
	28 per 100	12 per 100 (8 to 18)				
Weight gain during pregnancy	The mean weight gain during pregnancy was 0	The mean weight gain during pregnancy in the intervention group was 0.64 more (0.41 fewer to 1.7 more)	-	411 (2 RCTs)	⊕⊝⊝⊝ VERY LOW [2 3 4]	D'Anna 2015 included obese pregnant women and D'Anna 2013 included non-obese women with a family history of type 2 diabetes Random-effects model
Hypertensive disorders of pregnancy	Study population		RR 0.43 (0.02 to 8.41)	398 (2 RCTs)	⊕⊝⊝⊝ VERY LOW [2 5 6]	Random-effects model
	4 per 100	2 per 100 (0 to 33)				
Caesarean section	Study population		RR 0.95 (0.76 to 1.19)	398 (2 RCTs)	⊕⊕⊝⊝ LOW [2 6]	
	45 per 100	43 per 100 (34 to 54)				
Perineal trauma			Not estimable	(0 studies)		No data reported for perineal trauma in any of the included studies

Postnatal depression		Not estimable	(0 studies)	No data reported for postnatal depression in any of the included studies
Type 2 diabetes		Not estimable	(0 studies)	No data reported for type 2 diabetes in any of the included studies

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded (-1) due to unclear risk of bias for allocation concealment in two of the included trials (one trial did not provide sufficient detail to determine allocation concealment and one trial (reported as a conference abstract) had no details of random sequence generation, allocation concealment or blinding) and for high risk of performance bias for lack of blinding (two trials were open-label trials with no blinding of participants or researchers, however one trial explicitly described blinding of outcome assessors and was assessed as low risk of detection bias).
[2] Studies were conducted in Italy with Caucasian women and generalisability of findings is limited, downgraded (-1).
[3] Evidence of imprecision with wide confidence intervals crossing the line of no effect, downgraded (-1).
[4] Heterogeneity high with I^2 = 54% (indirectness) probably due to different study populations, downgraded (-1).
[5] Wide confidence intervals with very low event rates and a small sample size suggest evidence of imprecision, downgraded (-1).
[6] Downgraded (-1) due to insufficient evidence to judge allocation concealment in one trial and subsequent judgement of unclear risk of bias. The other trial had a low risk of bias for allocation concealment. Both trials were open-label with no blinding of participants or researchers, although one trial explicitly stated that outcome assessors were blinded to treatment allocation.

Summary of findings 2. Myo-inositol for preventing gestational diabetes (neonatal, child and adult outcomes)

Antenatal supplementation with myo-inositol for preventing gestational diabetes

Patient or population: pregnant women who were at risk of GDM

Setting: Italy
Intervention: Myo-inositol
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Myo-inositol				
Large-for-gestational age			not estimable	(0 studies)		No data reported for large-for-gestational age in any of the included studies
Perinatal mortality			not estimable	(0 studies)		No data reported for perinatal mortality in any of the included studies
Composite of serious neonatal outcomes			not estimable	(0 studies)		No data reported for composite of serious neonatal outcomes in any of the included studies
Neonatal hypoglycaemia	Study population		RR 0.36 (0.01 to 8.66)	398 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
	0 per 100	0 per 100 (0 to 4)				
Adiposity			not estimable	(0 studies)		No data reported for adiposity in any of the included studies
Diabetes			not estimable	(0 studies)		No data reported for diabetes in any of the included studies
Neurosensory disability			not estimable	(0 studies)		No data reported for neurosensory disability in any of the included studies

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] No blinding in either study and reporting of allocation concealment was unclear in one of the studies, downgraded (-1).
[2] Both studies were conducted in Italy with Caucasian women and may not be generalisable to other settings, downgraded (-1).
[3] Wide confidence intervals with very low event rates suggest evidence of imprecision, downgraded (-1).

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). GDM imposes several complications for affected women and their babies making it crucial for effective strategies for prevention.

Screening for, and diagnosis of GDM, usually undertaken between 24 and 28 weeks' of pregnancy, varies from country to country, with some countries selectively screening based on risk factors (NICE 2015), and other countries using universal screening of all pregnant women (Nankervis 2013). If thresholds for the oral glucose challenge test (OGCT) are exceeded, a diagnostic oral glucose tolerance test (OGTT) is used to confirm diagnosis, or a diagnostic OGTT can be used without screening by OGCT (MoH 2014).

A number of risk factors are associated with developing gestational diabetes mellitus (Nankervis 2013):

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

Several studies have reported an increasing prevalence of GDM (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 increases the risk of serious injury at birth, the likelihood of caesarean delivery, and the incidence of newborn intensive care unit (NICU) admission (Ali 2011). Infants of women with GDM are at increased risk of developing obesity, impaired glucose tolerance, 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). A recently published review '*Diet and exercise interventions for preventing gestational diabetes mellitus'* assessing the effects of physical exercise in combination with dietary advice for pregnant women for preventing GDM, and health consequences for the mother and her infant/child (Bain 2015), found no clear differences in outcomes between women receiving diet and exercise interventions compared with those receiving no intervention.

Metformin, an oral anti-diabetic drug in the biguanide class, is the first-line drug of choice for the treatment of type 2 diabetes (Nankervis 2013). Metformin has been used to prevent GDM in pregnant women with a history of polycystic ovary syndrome (PCOS) with contrasting results (Glueck 2008; Tang 2012). A recent trial on the effect of metformin on obese pregnant women found that while fasting glucose and insulin were lower at 28 weeks' gestation in the metformin group, there was no difference in the risk of developing gestational diabetes, by either IADSPG or WHO criteria, between those women who received metformin and those who received placebo (Chiswick 2015).

Myo-inositol is a nutrient the body requires for cell membrane formation and cellular reactions to environmental messages (Croze 2013). 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, legumes and nuts (Croze 2013).

Due to its role as a second messenger, myo-inositol has many benefits. When used as a co-treatment in patients with subclinical hypothyroidism and autoimmune thyroiditis, it aided in maintaining euthyroidism (normal production of thyroid hormone) (Nordio 2013). Myo-inositol has been associated with an improvement in premenstrual dysphoric disorder (PMDD), a mood disorder disrupting the social and/or occupational life of affected women (Carlomagno 2011). Myo-inositol has also been associated with improvements in a range of symptoms of PCOS, a medical condition characterised by insulin resistance (Papaleo 2007). Inositol has been associated with improvements in insulin sensitivity and ovulatory function in young women affected by PCOS (Genazzani 2008; Nestler 1999). Furthermore, myo-inositol has been associated with improvements in hyperandrogenism in women with PCOS (Minozzi 2008), and increased number and quality of oocytes in women undergoing IVF treatment for a previous history of infertility (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 with the control group (n = 45) (Corrado 2011). A retrospective review of 46 pregnant women treated with myo-inositol compared with 37 controls described it as safe during the pre-pregnancy and early pregnancy period when used in insulin-resistant conditions (D'Anna 2012). 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.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials and conference abstracts assessing the effects of myo-inositol for the prevention of gestational diabetes mellitus (GDM) were considered for inclusion. We planned to include cluster-randomised trials but none were identified. Quasi-randomised trials and cross-over trials were not eligible for inclusion.

Types of participants

Trials that recruited pregnant women. Women with pre-existing type 1 or type 2 diabetes were excluded.

Types of interventions

The intervention includes administration of any doses of myo-inositol in pregnancy, alone or in a combination preparation, for the purpose of preventing GDM. We included studies where such intervention was compared with those who received no treatment, placebo or another intervention.

Types of outcome measures

Primary outcomes

Maternal outcomes

1. Gestational diabetes mellitus (diagnostic criteria as defined in individual trials)
2. Hypertensive disorders of pregnancy (including pre-eclampsia, eclampsia, pregnancy-induced hypertension)

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)

Secondary outcomes

Maternal outcomes

1. Caesarean section
2. Placental abruption
3. Induction of labour
4. Perineal trauma
5. Postpartum haemorrhage
6. Postpartum infection
7. Weight gain during pregnancy
8. Adherence to the intervention (as defined by trialists)
9. Behaviour changes associated with the intervention (as defined by trialists)
10. Relevant biomarker changes associated with the intervention (e.g. adiponectin, free fatty acids, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL), insulin)
11. Sense of well-being and quality of life
12. Views of the intervention
13. Breastfeeding (e.g. at discharge, six weeks postpartum)
14. Adverse effects of intervention

Long-term maternal outcomes

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

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
13. Shoulder dystocia
14. Bone fracture
15. Nerve palsy
16. Respiratory distress syndrome
17. Hypoglycaemia (variously defined)
18. Hyperbilirubinaemia

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 I diabetes mellitus
7. Type II diabetes mellitus
8. Impaired glucose tolerance
9. Dyslipidaemia or metabolic syndrome
10. Neurodisability
11. 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 BP, hypertension, cardiovascular disease, metabolic syndrome)
5. Type I diabetes mellitus
6. Type II 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 (NICU) 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
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 searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (2 November 2015).

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 which has been fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports. The search terms used are given in Appendix 1.

Searching other resources

We searched reference lists of retrieved studies.

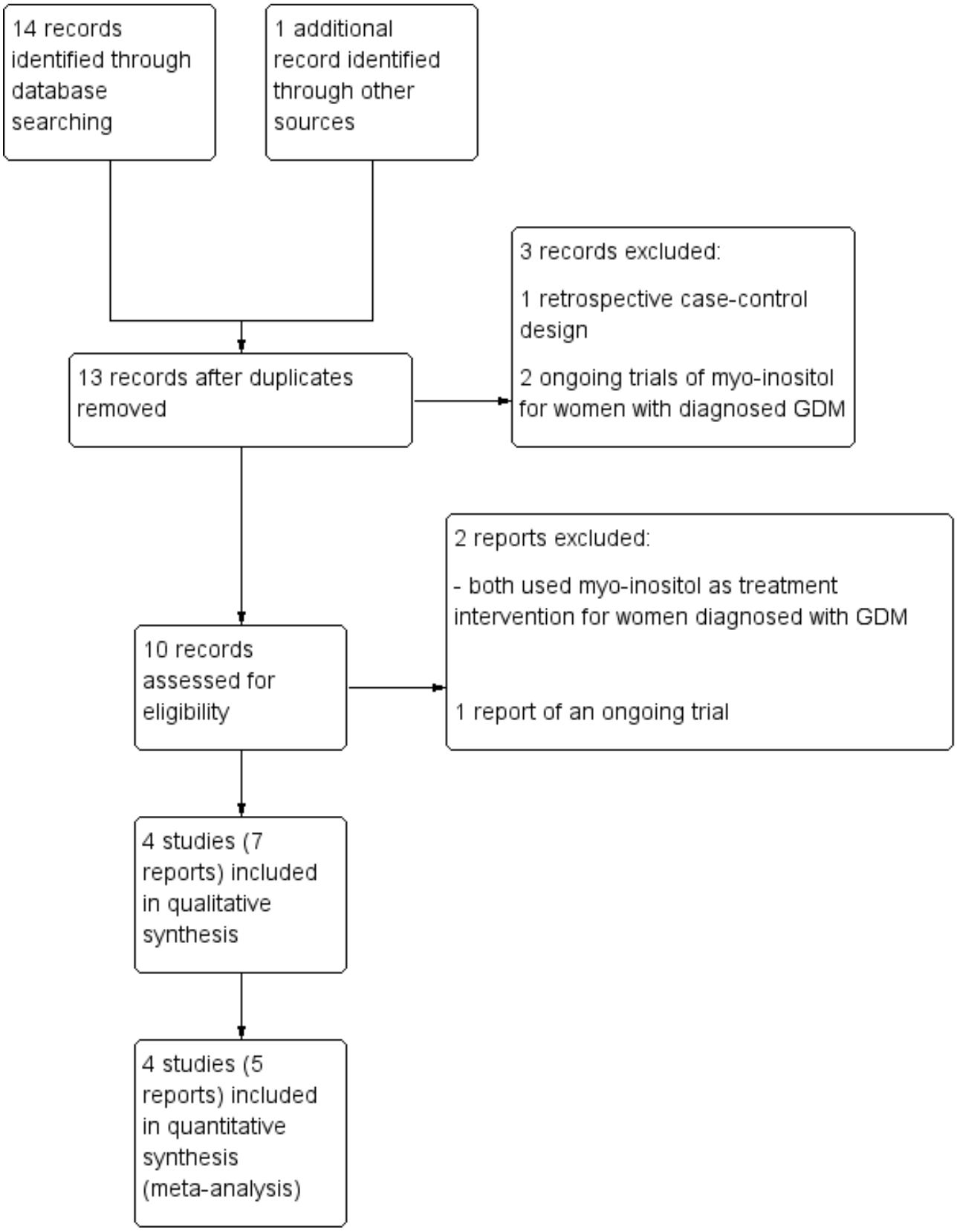
We did not apply any language or date restrictions.

Data collection and analysis

Selection of studies

Two review authors (TC and JB) independently assessed for inclusion all the potential studies identified as a result of the search strategy. We resolved any disagreement through discussion. We created a study flow diagram (Figure 1) to map out the number of records identified, included and excluded.

Figure 1. -Study flow diagram.



Data extraction and management

We designed a form to extract data based on the Cochrane Pregnancy and Childbirth Group's data extraction form. For eligible studies, two review authors (TC and JB or JA) independently extracted the data using the agreed form. We resolved discrepancies through discussion. Data were entered into Review Manager software (RevMan 2014) and checked for accuracy. When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion.

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

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

We assessed 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 described 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 assessed 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 described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated 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 was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed the 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 described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed 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 described for each included study any important concerns we have about other possible sources of bias.

We assessed 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 made 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 assessed the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. We explored 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

We assessed the quality of the evidence 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 for the main comparisons.

Maternal

1. Diagnosis of GDM
2. Gestational weight gain
3. Hypertensive disorders of pregnancy (including pre-eclampsia, eclampsia, pregnancy-induced hypertension)
4. Caesarean section
5. Perineal trauma
6. Postnatal depression
7. Development of subsequent type II diabetes mellitus

Neonatal, child, adult outcomes

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

We used 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 was 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 presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference with 95% confidence intervals. We planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods, again with 95% confidence intervals.

Unit of analysis issues

Cluster-randomised trials

No cluster-randomised trials were identified for inclusion in this review. If cluster-randomised trials are identified for inclusion in future updates of this review, they will be included 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 present maternal data as per woman randomised and neonatal data per infant.

Multiple arm studies

In future updates of this review, 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 noted levels of attrition. We planned to 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 carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were 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 was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

As there were only four studies identified we did not undertake investigation of reporting biases. In future updates of this review, if 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 carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analyses for combining data where it was 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 was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

Where we used random-effects analyses, the results are 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 identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses where data were available. We considered whether an overall summary was meaningful, and if it was, used random-effects analysis to produce it.

We planned to conduct the following subgroup analyses, but were unable to split the participant data into subgroups and none of the included trials commenced supplementation with myo-inositol pre-pregnancy.

1. Polycystic ovary syndrome (PCOS) women versus non-PCOS women
2. Obese women versus non-obese women
3. Dosage - high versus low dose
4. Myo-inositol alone or in combination versus non myo-inositol combination
5. Commencement of myo-inositol supplementation - pre-pregnancy versus first trimester

We planned to restrict subgroup analysis to this review's primary outcomes.

In future versions of this review, 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

We had insufficient trials to conduct sensitivity analysis for this review. If in future updates there are sufficient trials for analysis, and there is evidence of significant heterogeneity for primary outcomes, we will explore heterogeneity by using the quality of the included trials. 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.

RESULTS

Description of studies

Results of the search

See: Figure 1.

We assessed 15 trial reports, two were duplicates, three were screened out at title and abstract stage. Four trials (seven reports) are included, two are excluded and we added one to Ongoing studies.

Included studies

Study design

We included four randomised controlled trials, three published trials (D'Anna 2013; D'Anna 2015; Malvasi 2014) and a conference abstract (Facchinetti 2013).

Setting

All trials were conducted in Italy.

Participants

All trials were conducted in pregnant women.

Gestational age at trial entry

1. < 11 weeks' gestation (Facchinetti 2013)
2. 12 to 13 weeks' gestation (D'Anna 2013; D'Anna 2015)
3. 13 to 24 weeks' gestation (Malvasi 2014)

Body mass index (BMI)

1. < 30 kg/m^2 (D'Anna 2013)
2. ≥ 30 kg/m^2 (D'Anna 2015)
3. > 27 kg/m^2 (Facchinetti 2013)
4. Between 25 and 30 kg/m^2 (Malvasi 2014)

Groups were comparable at baseline for age, parity, BMI and haematological parameters in Malvasi 2014. In both D'Anna 2015 and D'Anna 2013, the participants were comparable between groups at baseline for maternal age, gestational age at commencement of treatment and gestational age at time of oral glucose tolerance test (OGTT). D'Anna 2013 included women exclusively of Caucasian ethnicity. Ethnicty is not mentioned in the inclusion criteria in D'Anna 2015; Facchinetti 2013 and Malvasi 2014. An inclusion criterion in D'Anna 2013 was a first-degree relative with type 2 diabetes. Women with pre-existing diabetes mellitus were excluded from D'Anna 2013, D'Anna 2015, and Malvasi 2014.

Intervention and comparison

Myo-inositol dose

The following doses of myo-inositol were reported.

1. 4 g myo-inositol plus 400 mcg folic acid daily in divided doses (2 g myo-inositol plus 200 mcg folic acid twice a day) (D'Anna 2013; D'Anna 2015; Facchinetti 2013)
2. 2 g myo-inositol, 400 mg d-chiro-inositol, 400 mcg folic acid and 10 mg manganese per day in one dose (Malvasi 2014)

Comparison

The following comparisons were reported.

1. 200 mcg folic acid (D'Anna 2013; D'Anna 2015)
2. Folic acid dose not stated (Facchinetti 2013)
3. No description of what constituted the 'placebo' administered to the control group (Malvasi 2014)

D'Anna 2015 provided nutritional and lifestyle counselling to women in both the treatment and control group. None of the other included trials detailed the provision of any nutritional or lifestyle counselling to their participants.

Diagnostic criteria used to diagnose GDM

1. International Association of Diabetes and Pregnancy Study Groups (IADPSG 2010): (D'Anna 2013; D'Anna 2015)
2. Not stated: (Facchinetti 2013; Malvasi 2014)

Outcomes

Three trials reported on gestational diabetes mellitus and provided fasting, one- and two-hour blood glucose results (D'Anna 2013; D'Anna 2015; Facchinetti 2013). Two trials reported a number of maternal and infant outcomes such as hypertensive disorders of pregnancy, caesarean section, weight gain during pregnancy, adverse effects of intervention, gestational age at birth, preterm birth, macrosomia, birthweight, shoulder dystocia and neonatal hypoglycaemia (D'Anna 2013; D'Anna 2015).

One trial reported on relevant biomarker changes associated with the intervention (Malvasi 2014), and only one trial reported on neonatal respiratory distress syndrome (D'Anna 2013).

Funding sources

Three trials did not state the source of funding (D'Anna 2013; Facchinetti 2013; Malvasi 2014). D'Anna 2015 was funded by a grant from Messina Univeristy, Italy. Two trials reported that none of the authors had any potential financial conflicts of interest (D'Anna 2015; Malvasi 2014).

Ongoing studies

One ongoing trial using myo-inositol 4 g plus folic acid 400 mcg as the intervention and folic acid 400 mcg as the control has been identified for potential inclusion in an update of this review when it is published (Farren 2013) (See Ongoing studies).

Excluded studies

Two studies were excluded (Corrado 2011; Matarrelli 2013) as they did not use myo-inositol as a preventative intervention in women at risk of developing gestational diabetes, but rather used myo-inositol as a treatment for women already diagnosed with gestational diabetes. See Characteristics of excluded studies.

Risk of bias in included studies

The overall risk of bias appears to be 'unclear', in part due to the insufficient information provided in Facchinetti 2013 and Malvasi 2014 to make an assessment of risk of bias, and part due to the lack of blinding of participants and clinicians in D'Anna 2013 and D'Anna 2015. Refer to Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

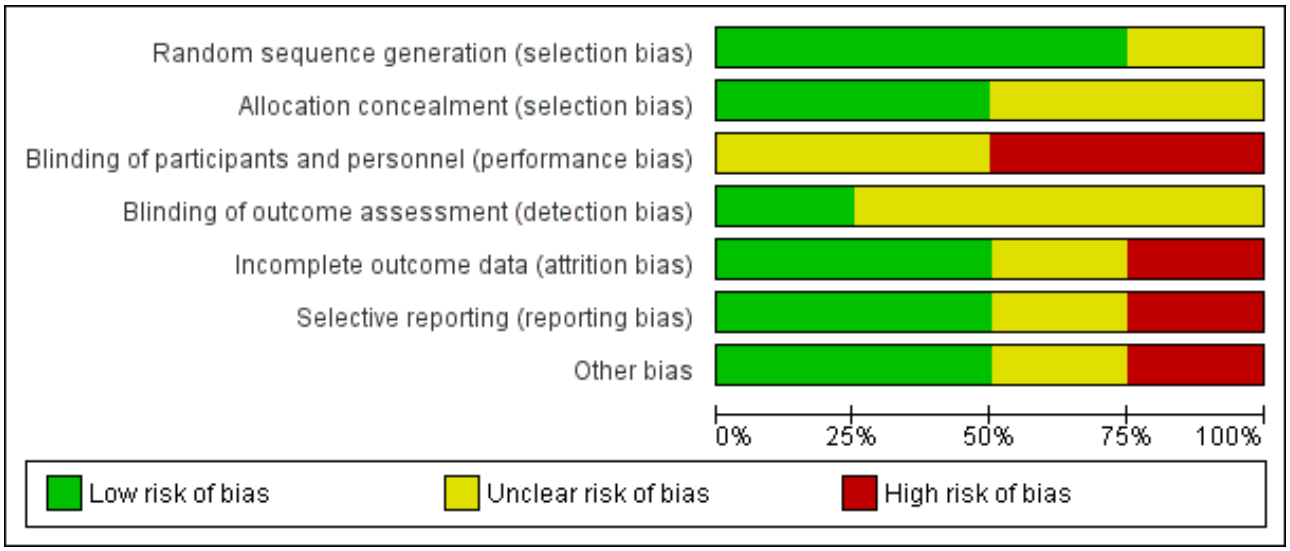
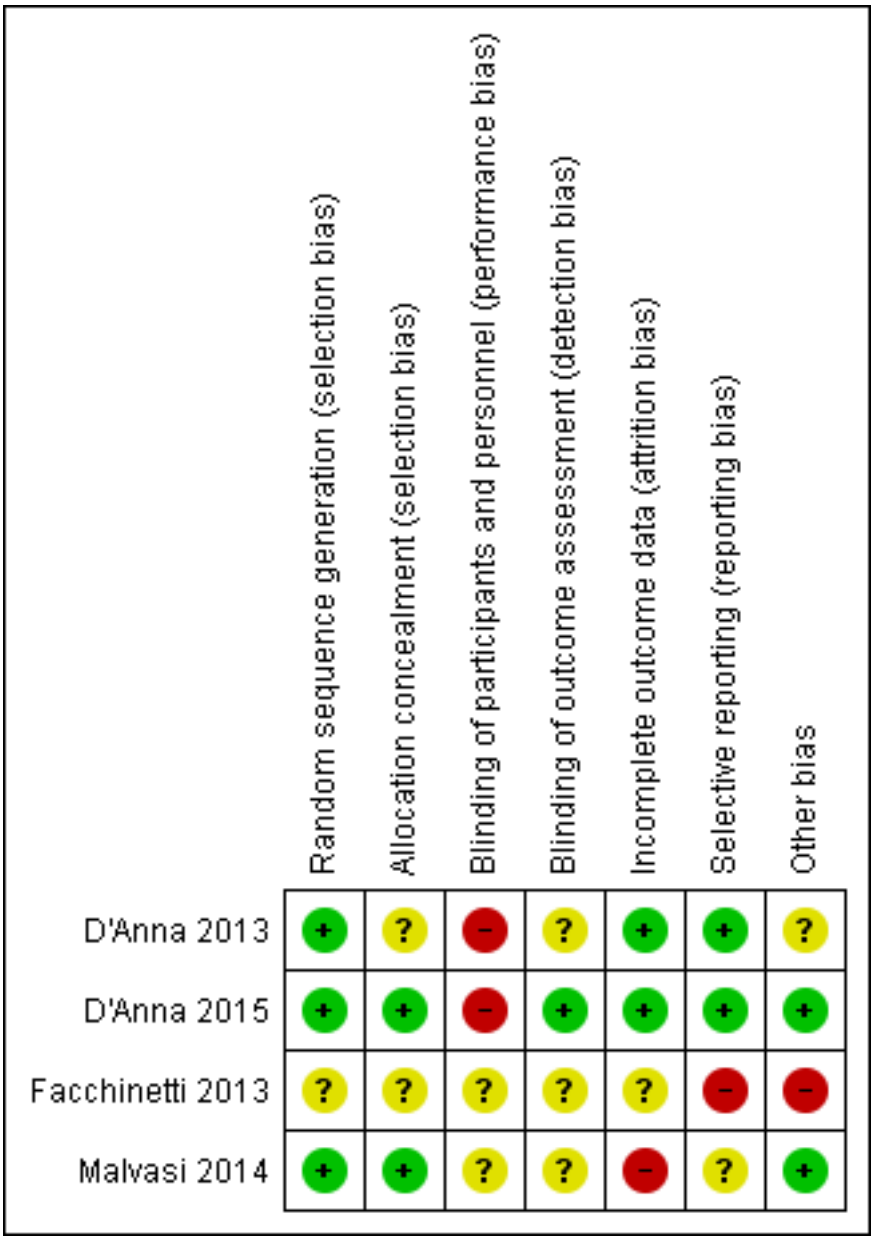


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two trials used a computer-generated random sequence (D'Anna 2015, D'Anna 2013), and one used a random number table (Malvasi 2014) and were assessed as having a low risk of selection bias. Facchinetti 2013 stated the participants were randomised but the abstract did not provide any further information on the method of sequence generation. Consequently, this trial was assessed as having an unclear risk of selection bias.

The method of allocation concealment was not stated in two of the trials (D'Anna 2013; Facchinetti 2013), and these were assessed as having an unclear risk of bias. D'Anna 2015 and Malvasi 2014 described allocation assignment by a centralised contact who was independent of the recruitment process these were assessed as low risk of bias.

Blinding

Facchinetti 2013 did not provide sufficient information to make a judgement and was assessed as having an unclear risk of bias. D'Anna 2013 states that the trial was open label with blinding not being undertaken. This was assessed as having a high risk of performance bias. Neither of these trials described blinding of outcome assessment and both were therefore assessed as having an unclear risk of detection bias. Whilst the outcome of incidence of gestational diabetes is diagnosed by blood test and is unlikely to be affected by blinding, other outcomes such as neonatal respiratory distress syndrome are more subjective and may be impacted by knowledge of treatment group.

D'Anna 2015 was an open-label trial and was assessed as high risk for performance bias. However, researchers collecting data were blinded to allocation group and the primary outcome was

an objective measurement of laboratory values. This study was assessed as having a low risk of detection bias.

Malvasi 2014 blinded participants but the clinicians involved were aware of the treatment allocation. This was assessed as an unclear risk of performance bias. No mention was made of blinding of outcome assessors and was therefore assessed as having an unclear risk of detection bias.

Incomplete outcome data

D'Anna 2015, and D'Anna 2013 were assessed as having a low risk of attrition bias for minimal losses to follow-up. There was 9% overall loss to follow-up in D'Anna 2015, and 10% overall loss to follow-up in D'Anna 2013.

Malvasi 2014 was assessed as having a high risk of attrition bias due to 26% overall attrition (17 women excluded from final analysis). Seven women left the trial spontaneously but their group allocation, or reasons for withdrawing were not stated.

Facchinetti 2013 was assessed as having an unclear risk of attrition bias as it was an interim analysis at 50% of recruitment and it is unclear how many women had been recruited at that point as the denominator is not stated.

Selective reporting

Two trials were assessed as having a low risk of reporting bias as all pre-specified outcome measures were reported on (D'Anna 2015; D'Anna 2013). While Malvasi 2014 reported on all pre-specified outcomes, it was assessed as having an unclear risk of reporting bias as blood glucose concentration was not specified if it was fasting or post prandial and the results were not able to be included in the analysis. In addition, this trial did not include any pregnancy outcome or neonatal results.

One trial was assessed as having a high risk of bias as primary as secondary outcomes were not stated, and only OGTT results and the incidence of GDM were reported (Facchinetti 2013).

Other potential sources of bias

Facchinetti 2013 was assessed as being at high risk of other bias, as it was available only as a conference abstract. D'Anna 2013 has an unclear risk of other bias for stating in the manuscript that intention-to-treat analysis was conducted on the available data, but only per-protocol analysis is published. D'Anna 2015 and Malvasi 2014 were both assessed as being at a low risk of 'other' bias.

Effects of interventions

See: **Summary of findings for the main comparison** Myo-inositol for preventing gestational diabetes maternal outcomes (maternal outcomes); **Summary of findings 2** Myo-inositol for preventing gestational diabetes (neonatal, child and adult outcomes)

The quality of the evidence of the included studies is summarised in the Summary of findings for the main comparison and Summary of findings 2 for the pre-specified outcomes of this review.

1.0 Myo-inositol versus control

Four trials were identified that compared myo-inositol and control groups who received 'placebo' (D'Anna 2015; D'Anna 2013; Facchinetti 2013; Malvasi 2014).

Maternal primary outcomes

1.1 Gestational diabetes mellitus

For the mother, myo-inositol was associated with a reduction in the incidence of gestational diabetes mellitus (GDM) compared with control (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.29 to 0.64; three trials; n = 502 women) (D'Anna 2013; D'Anna 2015; Facchinetti 2013) (Analysis 1.1).

Using the GRADEpro Guideline Development Tool, the quality of the evidence was considered to be *low* due to issues around risk of bias and indirectness. For women who received myo-inositol, the risk of GDM ranged from 8% to 18%; for women in the control group, the risk of GDM was 28%.

Three studies reported on blood glucose concentrations at the time of the diagnostic 75 g oral glucose tolerance test at 24 to 28 weeks' gestation. Myo-inositol was associated with a reduction in blood glucose concentrations compared to the control group.

1. Fasting: mean difference (MD) -0.20 mmol/L, 95% CI -0.28 to -0.12; three trials; n = 502 women; Analysis 1.2.
2. One hour: MD -0.68 mmol/L, 95% CI -1.00 to -0.37; three trials; n = 502 women; Analysis 1.3.
3. Two hours: MD -0.75 mmol/L, 95% CI -1.07 to -0.43; three trials; n = 502 women; Analysis 1.4.

1.2 Hypertensive disorders of pregnancy (including pre-eclampsia, eclampsia, pregnancy-induced hypertension)

Two trials reported on hypertensive disorders of pregnancy (D'Anna 2013; D'Anna 2015). There was no clear difference in the risk of gestational hypertension between women treated with myo-inositol and those receiving a 'placebo' (average RR 0.43, 95%CI 0.02 to 8.41; two trials, n = 398 women; random-effects model used; $Tau^2 = 3.23$; $I^2 = 69\%$) (Analysis 1.5). Using the GRADEpro Guideline Development Tool, the quality of the evidence was considered to be*very low* due to issues around risk of bias, imprecision and indirectness. For women who received myo-inositol, the risk of hypertensive disorders of pregnancy ranged from 0% to 33%; for women in the control group, the risk of was 4%. Heterogeneity is most likely explained through the different populations recruited into the trials. The inclusion criteria for D'Anna 2015 was for obese pregnant women and D'Anna 2013 recruited women who were not obese but had a family history of type 2 diabetes. Additionally, nutritional and lifestyle counselling was provided to both the intervention and control groups in D'Anna 2015, but was not provided in D'Anna 2013.

Neonatal primary outcomes

Large-for-gestational age

None of the included trials reported data on the primary neonatal outcome of large-for-gestational age.

Perinatal mortality

None of the included trials reported data on the primary neonatal outcome of perinatal mortality.

Mortality or morbidity composite (variously defined by trials, e.g. infant death, shoulder dystocia, bone fracture or nerve palsy)

None of the included trials reported data on the primary neonatal outcome of death or morbidity composite.

Maternal secondary outcomes

Caesarean section

There was no clear difference in the risk of caesarean section between the myo-inositol and control groups (RR 0.95, 95% CI 0.76 to 1.19; two trials; n = 398 women) (D'Anna 2013; D'Anna 2015) (Analysis 1.6).

Using the GRADEpro Guideline Development Tool, the quality of the evidence was considered to be *low* due to issues around risk of bias and indirectness. For women who received myo-inositol, the risk of birth by caesarean section ranged from 34% to 54%; for women in the control group, the risk of having a caesarean section was 45%.

Weight gain during pregnancy

There was no difference in weight gain during pregnancy between those women who received myo-inositol supplementation compared with those in the control group (MD 0.64 kg, 95% CI -0.41 to 1.70; two trials; n = 411 women, random-effects model, $Tau^2 = 0.33$, $I^2 = 54\%$) (D'Anna 2013; D'Anna 2015) (Analysis 1.7). Using the GRADEpro Guideline Development Tool, the quality of the evidence was considered to be *very low* due to issues around risk of bias, imprecision and indirectness. Heterogeneity is most likely explained through the different populations recruited into the trials. The inclusion criteria for D'Anna 2015 was for obese pregnant women and D'Anna 2013 recruited women who were not obese but had a family history of type 2 diabetes. Additionally, nutritional and lifestyle counselling was provided to both the intervention and control groups in D'Anna 2015, but was not provided in D'Anna 2013.

Relevant biomarker changes associated with the intervention

One trial reported on relevant biomarkers (Malvasi 2014) (Analysis 1.8). Myo-inositol was associated with reduced total cholesterol (MD -47.29 mg/dL, 95%CI -52.87 to -41.71; one trial, n = 48 women), low-density lipoproteins (LDL) (MD -33.50 mg/dL, 95%CI -39.71 to -27.29; one trial, n = 48 women), high-density lipoproteins (HDL) (MD -13.79 mg/dL, 95%CI -18.91 to -8.67; one trial, n = 48 women), and triglycerides (MD -39.33 mg/dL, 95%CI -44.00 to -34.66; one trial, n = 48 women) compared with the control group.

Adverse effects of intervention

There were no adverse effects of therapy in the two trials that reported on this outcome (D'Anna 2013; Malvasi 2014). The remaining two trials did not report on adverse effects (D'Anna 2015; Facchinetti 2013).

Other secondary outcomes

No data were reported for any of the other pre-specified maternal secondary outcomes for this systematic review (placental abruption, induction of labour, perineal trauma, postpartum haemorrhage, postpartum infection, adherence to the intervention (as defined by trialists), behaviour changes associated with the intervention (as defined by trialists), sense of well-being and quality of life, views of the intervention, breastfeeding (e.g. at discharge, six weeks postpartum), postnatal depression, postnatal weight retention or return to pre-pregnancy weight, body mass index (BMI), gestational diabetes mellitus in a subsequent pregnancy, type I diabetes, type 2 diabetes, impaired glucose tolerance or cardiovascular health (as defined by trialists, including blood pressure (BP), hypertension, cardiovascular disease, metabolic syndrome)).

Other outcomes not pre-specified

Although the main aim of the included studies was the prevention of GDM, two of the included trials that continued the intervention until the end of pregnancy reported on the need for additional pharmacological therapy (D'Anna 2013; D'Anna 2015). For interest we include a summary of these data. There was no difference between the myo-inositol and control groups for the need for supplementary insulin therapy (RR 0.48, 95% CI 0.11 to 2.09; two trials; n = 398 women (Analysis 1.10)).

Neonatal secondary outcomes (infant, child and adult)

There were no differences in secondary neonatal outcomes between infants of mothers supplemented with myo-inositol and the control groups.

Gestational age at birth

There was no difference in the gestational age at birth between myo-inositol and control groups (MD 5.50 days, -7.24 to 18.24; two trials; n = 398 infants; random-effects model, $Tau^2 = 81.58$, $I^2 = 97\%$) (D'Anna 2013; D'Anna 2015) (Analysis 1.11). Caution is required when interpreting the data due to significant heterogeneity ($I^2 = 97\%$). The difference is most likely due to differences in the populations. The inclusion criteria for D'Anna 2015 was for obese pregnant women and D'Anna 2013 recruited women who were not obese but had a family history of type 2 diabetes. Additionally, nutritional and lifestyle counselling was provided to both the intervention and control groups in D'Anna 2015, but was not provided in D'Anna 2013.

Preterm birth

There was no difference for the risk of preterm birth between the myo-inositol and the control groups (RR 0.45, 95% CI 0.17 to 1.14; two trials; n = 398 infants) (D'Anna 2013; D'Anna 2015) (Analysis 1.12).

Macrosomia

There was no clear difference between myo-inositol and control groups for the risk of macrosomia (RR 0.35, 95% CI 0.02 to 6.37; two trials; n = 398 infants; random-effects model, $Tau^2 = 3.33$, $I^2 = 73\%$) (D'Anna 2013; D'Anna 2015) (Analysis 1.13).

Caution is required when interpreting the data due to significant heterogeneity ($I^2 = 73\%$). The difference is most likely due to differences in the populations. The inclusion criteria for D'Anna 2015 was for obese pregnant women and D'Anna 2013 recruited women who were not obese but had a family history of type 2 diabetes. Additionally, nutritional and lifestyle counselling was provided to both the intervention and control groups in D'Anna 2015, but was not provided in D'Anna 2013.

Birthweight

There was no difference between myo-inositol and control groups for birthweight (MD -60.47 g, 95% CI -265.21 to 144.26; two trials; n = 398 infants; random-effects model, Tau^2 = 16609.07, I^2 = 76%) (D'Anna 2013; D'Anna 2015) (Analysis 1.14). No data were reported for birthweight z scores.

Caution is required when interpreting the data due to significant heterogeneity (I^2 = 76%). The difference is most likely due to differences in the populations. The inclusion criteria for D'Anna 2015 was for obese pregnant women and D'Anna 2013 recruited women who were not obese but had a family history of type 2 diabetes. Additionally, nutritional and lifestyle counselling was provided to both the intervention and control groups in D'Anna 2015, but was not provided in D'Anna 2013.

Shoulder dystocia

There was no difference between myo-inositol and control groups for the risk of shoulder dystocia (RR 2.33, 95% CI 0.12 to 44.30; two trials; n = 398 infants. Random-effects model used Tau^2 = 3.24%, I^2 = 72%) (D'Anna 2013; D'Anna 2015) (Analysis 1.15).

Caution is required when interpreting the data due to significant heterogeneity (I^2 = 72%). The difference is most likely due to differences in the populations. The inclusion criteria for D'Anna 2015 was for obese pregnant women and D'Anna 2013 recruited women who were not obese but had a family history of type 2 diabetes. Additionally, nutritional and lifestyle counselling was provided to both the intervention and control groups in D'Anna 2015, but was not provided in D'Anna 2013.

Respiratory distress syndrome

There was no difference between myo-inositol and control groups for the risk of respiratory distress syndrome (RR 0.99, 95% CI 0.06 to 15.60; one trial; n = 197 infants (D'Anna 2013).

Neonatal hypoglycaemia

There was no difference between myo-inositol and control groups for the risk of neonatal hypoglycaemia (RR 0.36, 95% CI 0.01 to 8.66; two trials; n = 398 infants) (D'Anna 2013; D'Anna 2015)(Analysis 1.17). Using the GRADEpro Guideline Development Tool, the quality of the evidence was considered to be *very low* due to issues around risk of bias, imprecision and indirectness. For infants of women who received myo-inositol, the risk of neonatal hypoglycaemia ranged from 0% to 4%; for infants of women in the control group, the risk of neonatal hypoglycaemia was 0%.

Other secondary outcomes

No other secondary neonatal (infant, child, adult) outcomes of this systematic review were reported (stillbirth, neonatal mortality, Apgar score < five at seven minutes, small-for-gestational age, head circumference and z score, length and z score, ponderal index, adiposity, bone fracture, nerve palsy, hyperbilirubinaemia. For the infant as a child and adult, no data were reported for any of the pre-specified outcomes (weight, height, adiposity (e.g. as measured by BMI, skinfold thickness), cardiovascular health (as defined by trialists, including BP, hypertension, cardiovascular disease, metabolic syndrome), type I diabetes, type 2 diabetes mellitus, impaired glucose tolerance, dyslipidaemia or metabolic syndrome, employment, education and social status/achievement).

Health service outcomes

One trial reported on admission to the neonatal intensive care unit (NICU) (D'Anna 2015). There was no difference in risk of admission to the NICU between myo-inositol and control groups (RR 0.09, 95% CI 0.01 to 1.70; one trial; n = 201 (D'Anna 2015).

None of the included trials reported any of the other health service outcomes (number of hospital or health professional visits (e.g. midwife, obstetrician, physician, dietitian, diabetic nurse), number of antenatal visits or admissions, length of antenatal stay, length of postnatal stay (mother), length of postnatal stay (baby), costs to families associated with the management provided, costs associated with the intervention, cost of maternal care, cost of offspring care).

DISCUSSION

Summary of main results

Although the evidence is based on four, small trials (three published trials and a conference abstract), it appears that myo-inositol shows promise in reducing the risk of gestational diabetes. None of the current trials reported on any of the primary neonatal outcomes of this review (large-for-gestational age, perinatal mortality or a composite of serious neonatal outcomes), and only two of the included trials reported on hypertensive disorders of pregnancy, one of the maternal primary outcomes of this review.

Overall completeness and applicability of evidence

The included trials were conducted in healthy women and those considered at high risk of developing gestational diabetes mellitus (GDM), including obese and non-obese women, and those with a family history of type 2 diabetes mellitus. However, applicability is limited by all trials being conducted in Italy amongst predominantly Caucasian women. Further trials in diverse settings, including participants of different ethnicities and varying risk factors would be useful in improving the applicability of the evidence. Not all of the outcomes of interest for this review were addressed in the included studies including pre-eclampsia, neonatal mortality, or longer-term maternal and infant health outcomes.

Quality of the evidence

The current available evidence is based on three randomised controlled trials, and a conference abstract that included a total of 567 women and their infants. Overall, there was unclear risk of bias due to insufficient information provided to enable a judgement of risk, particularly with regard to allocation concealment and blinding of outcome assessment. In addition, Facchinetti 2013 was only available as a conference abstract and was considered at high risk of publication bias.

Using the GRADE method, we assessed the quality of the body of evidence for the maternal outcomes of GDM, weight gain during pregnancy, hypertensive disorders of pregnancy, caesarean section, perineal trauma, postnatal depression and type 2 diabetes, and the neonatal outcomes of large-for-gestational age, perinatal mortality, composite of serious neonatal outcomes, neonatal hypoglycaemia, adiposity, diabetes and neurosensory disability. The GRADE method considers the risk of bias of the included studies, the directness of the evidence, consistency or

heterogeneity of the results, the precision of the effect estimates and the risk for publication bias. No data were reported for the maternal outcomes perineal trauma, postnatal depression and type 2 diabetes, or for the neonatal outcomes large-for-gestational age, perinatal mortality, composite of serious neonatal outcomes, adiposity, diabetes and neurosensory disability. The quality of the body of evidence was downgraded in the Summary of findings for the main comparison and Summary of findings 2 to *low* or *very low*. Two trials were open-label trials with no blinding of participants or clinicians (D'Anna 2013; D'Anna 2015). However, one trial did explicitly state that outcome assessors were blinded to treatment allocation (D'Anna 2015); the other trial lacked sufficient detail to determine allocation concealment (D'Anna 2013). One trial (reported as a conference abstract) had no details of random sequence generation, allocation concealment or blinding and was thus downgraded (Facchinetti 2013).

Potential biases in the review process

Multiple databases were searched by the Trials Search Co-ordinator of the Cochrane Pregnancy and Childbirth Group, without language or date restrictions in an attempt to limit bias by identifying all relevant trials. Where necessary, contact was made with authors to seek clarification or further information. As per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), two review authors appraised studies for inclusion, and extracted the data in order to minimise bias.

Agreements and disagreements with other studies or reviews

The increasing prevalence of GDM worldwide has led to greater interest in new and novel ways to prevent and treat GDM. The body of evidence for the use of antenatal myo-inositol supplementation for the prevention of GDM is still relatively small. Other literature (Di Benedetto 2013), and a systematic review (Rogozinska 2015) citing the trials included in this review, draw similar conclusions that myo-inositol shows significant potential to prevent GDM, with unanimous calls for larger, high-quality, randomised controlled trials to confirm this. As the body of randomised controlled trial evidence on the use of myo-inositol for prevention of GDM grows, we await the publication of ongoing trials that can be incorporated into future updates of this review.

AUTHORS' CONCLUSIONS

Implications for practice

Antenatal supplementation with myo-inositol for the prevention of GDM is a comparatively new and novel treatment. Whilst the results of this review indicate that myo-inositol shows promise in preventing the onset of GDM, there is currently insufficient evidence to support its routine adoption. The results of future research into the use of antenatal supplementation with myo-inositol for the prevention of GDM will provide more robust evidence for informing and guiding practice.

Implications for research

Although the currently available evidence indicates that antenatal supplementation with myo-inositol may be beneficial in reducing the incidence of GDM, the effect on important neonatal outcomes is unclear. Further well-designed randomised controlled trials are required, and should be sufficiently powered to detect differences in relevant maternal and neonatal outcomes. They should include participants of varying ethnicities and with various risk factors for GDM, such as obesity, polycystic ovarian syndrome, family history, and previous GDM, and explore the optimal dose, frequency and timing of supplementation. It is important that trials report on potential harms including adverse effects. In view of the availability of myo-inositol as a dietary supplement and its relatively low cost compared with traditional interventions for preventing GDM, future randomised controlled trials should include an economic analysis, or at least report on health service use and costs. If the efficacy of antenatal supplementation with myo-inositol compared with placebo is established, then it will also be useful to conduct trials that compare the use of myo-inositol with other preventative interventions such as lifestyle (diet and exercise) or pharmacological interventions such as metformin.

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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 for preventing gestational diabetes due to the attempt to have consistent outcomes for reviews on this condition.

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As part of the pre-publication editorial process, this review 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

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

D'Anna 2013

Methods	Type of study: parallel, randomised controlled trial.
Participants	220 women from Italy. Eligibility criteria: first-degree relative (mother, father or both) affected by type 2 diabetes, prepregnancy BMI < 30 kg/m^2, fasting plasma glucose < 126 mg/dL and random glycaemia < 200 mg/dL, singleton pregnancy, Caucasian. Women were 12-13 weeks' gestation at trial entry. Exclusion criteria: pre-pregnancy BMI ≥ 30 kg/m^2, previous GDM, pre-gestational diabetes, first trimester glycosuria, first-degree relative (mother or father) not affected by type 2 diabetes, fasting plasma glucose ≥ 126 mg/dL or random glycaemia ≥ 200 mg/dL, twin pregnancy, associated therapy with corticosteroids, polycystic ovarian syndrome. Location: Department of Gynecology and Obstetrics, University of Messina, Messina, Italy. Timeframe: 2010-2012.
Interventions	Intervention: 4 g myo-inositol plus 400 mcg folic acid daily (2 g myo-inositol plus 200 mcg folic acid twice a day) (n = 110). Duration of myo-inositol supplementation: from trial entry until the end of pregnancy. Comparison: 400 mcg folic acid daily (200 mcg folic acid twice a day) as 'placebo' (n = 110).
Outcomes	Maternal: incidence of GDM, gestational hypertension, caesarean section. Criteria used to diagnose GDM: IADPSG. Infant: fetal macrosomia (> 4000 g), preterm birth, shoulder dystocia, neonatal hypoglycaemia, respiratory distress syndrome.
Notes	Sample size calculation: not stated. Intention-to-treat analysis: yes (carried out but not reported). Losses to follow-up: 11 women in the intervention group, and 12 in the comparison group.

D'Anna 2013 *(Continued)*

	Funding: source of funding not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer randomization was used."
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial. Blinding not carried out.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Primary outcome of incidence of GDM diagnosed by blood test so blinding unlikely to impact assessment of this outcome. However, other secondary outcomes are more subjective.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall 10% loss to follow-up.
Selective reporting (reporting bias)	Low risk	All pre-specified outcome measures were reported on.
Other bias	Unclear risk	Intention-to- treat analysis was carried out on the available data, but was not reported in the manuscript.

D'Anna 2015

Methods	Type of study: parallel, randomised controlled trial.
Participants	220 obese pregnant women from Italy. Eligibility criteria: pre-pregnancy BMI ≥ 30 kg/m^2, singleton gestation. Women were 12-13 weeks' gestation at trial entry. Exclusion criteria: previous GDM, pre-gestational diabetes, first trimester glycosuria (urine glucose value 10 mg/dL or greater), first trimester fasting plasma glucose 126 mg/dL or greater, or random plasma glucose 200 mg/dL or greater, concomitant treatment with corticosteroids, hypertension or renal or hepatic disease. Location: obstetric departments of 2 university hospitals located in Messina and Modena, Italy. Timeframe: January 2011 - April 2014.
Interventions	Intervention: 4 g myo-inositol plus 400 mg folic acid daily (2 g myo-inositol + 200 mg folic acid orally twice a day), and nutritional and lifestyle counselling (n = 110). Duration of myo-inositol supplementation: from trial entry until the end of pregnancy. Comparison: 400 mg folic acid daily (200 mg folic acid orally twice a day), and nutritional and lifestyle counselling (n = 110).

D'Anna 2015 *(Continued)*

Outcomes	Maternal: occurrence of GDM, changes of insulin resistance from the first trimester to the performance of the OGTT performed at 24-28 weeks as measured by the homeostasis model assessment of insulin resistance, caesarean section, gestational hypertensive disorders. Criteria used to diagnose GDM: IADPSG. Infant: preterm delivery, shoulder dystocia, macrosomia (birthweight > 4000 g), neonatal hypoglycaemia, neonatal transfer to intensive care unit.
Notes	Sample size calculation was conducted. Intention-to-treat analysis. Funded by a grant from Messina University. The authors did not report any potential financial conflicts of interest. ClinicalTrials.gov trial registration NCT01047982. Further information was received following email contact with the authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated random number list prepared by an investigator with no clinical involvement with the trial."
Allocation concealment (selection bias)	Low risk	"Allocation concealment was ensured by central randomization." "After the research investigator had obtained the patients consent, he telephoned a contact who was independent of the recruitment process for allocation assignment."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was open label so blinding of participants and clinicians was not possible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Data collectors were blinded to treatment allocation and the data came from the patients record." "objective measurements of primary laboratory outcomes."
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% loss to follow-up overall. More participants chose to drop out of the myo-inositol group (n = 8) than the 'placebo' group (n = 0).
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes are reported on.
Other bias	Low risk	Appears free of other bias. The authors do not report any potential conflicts of interest.

Facchinetti 2013

Methods	Type of study: randomised controlled trial, parallel, 1:2 ratio.
Participants	91 women from Italy. Eligibility criteria: pregnant women, BMI > 27 kg/m^2, normal glucose and HbA1c.

Facchinetti 2013 *(Continued)*

	Women were < 11 weeks' gestation at trial entry. Exclusion criteria: previous GDM, chronic disorder (not specified). Location: Messina, Italy. Timeframe: not stated. This is an interim report at 50% recruitment.
Interventions	Intervention: 4 g myo-inositol plus 400 mg folic acid daily (2 g myo-inositol + 200 mg folic acid orally twice a day), and diet counselling (n = 31). Duration of myo-inositol supplementation not stated. Comparison: 400 mg folic acid daily (200 mg folic acid orally twice a day), and diet counselling (n = 60).
Outcomes	Maternal: 75 g 2 hour OGTT result at 24 to 26 weeks, diagnosis of GDM. Criteria used to diagnose GDM: not stated. Infant: not stated.
Notes	Sample size calculation: not stated. Intention-to-treat analysis: not stated. Losses to follow-up: not stated. Funding: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States "randomized" but no further information provided.
Allocation concealment (selection bias)	Unclear risk	"Randomization was done at each centre." Unclear by whom.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details provided, but unlikely due to the nature of the therapy (myo-inositol + folic acid versus folic acid alone).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Interim analysis at 50% recruitment conducted on 31 participants in the intervention group, and 60 participants in the control group. Unclear how many will be recruited as target denominator is not stated
Selective reporting (reporting bias)	High risk	Primary and secondary outcomes are not stated, only reports on OGTT and GDM results.
Other bias	High risk	Conference abstract only, at high risk of publication bias. Groups appeared comparable at baseline.

Malvasi 2014

Methods	Parallel, randomised controlled trial.
Participants	65 pregnant women from Italy. Eligibility criteria: healthy pregnant women, aged between 30-40, between 13 and 24 weeks' gestation, BMI between 25-30 kg/m2. Exclusion criteria: diabetes mellitus, cardiovascular disease, chronic hypertension, autoimmune disease, dysthyroidism. Location: Bari, Italy. Timeframe: January to December 2012.
Interventions	Intervention: a combination of 2000 mg myo-inositol, 400 mg d-chiro-inositol, 400 mcg folic acid, 10 mg manganese. Duration of myo-inositol supplementation: 60 days. Comparison: not stated.
Outcomes	Maternal: total cholesterol, LDL, HDL, blood glucose. Criteria used to diagnose GDM: not stated. Infant: not stated.
Notes	Sample size calculation not stated. Funding not stated. The authors did not report any potential financial conflicts of interest. Authors were contacted and provided further information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation sequence was generated by a random number table.
Allocation concealment (selection bias)	Low risk	Allocation was controlled by an independent statistician who assigned numbered patients to groups using sealed numbered containers.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were blinded. Clinicians were aware of treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	65 women were initially enrolled, 17 of which were excluded – 6 did not meet inclusion criteria, 4 refused to participate, 7 left the study spontaneously. Analysis was conducted on the remaining 48 women.
Selective reporting (reporting bias)	Unclear risk	All pre-specified outcomes are reported on (total cholesterol, LDL, HDL, blood glucose). No other maternal, pregnancy or neonatal outcomes are specified or reported.

Malvasi 2014 *(Continued)*

Other bias	Low risk	Appears free of other bias. The authors do not report any potential conflicts of interest.

BMI: body mass index
GDM: gestational diabetes mellitus
g: grams
HbA1c: Glycated haemoglobin
HDL: high density lipoprotein
IADPSG: International Association of Diabetes and Pregnancy Study Groups
kg/m2: kilograms per metre squared
LDL: low density lipoprotein
mcg: micrograms
mg/dL: milligrams per decilitre
OGTT: oral glucose tolerance test

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Corrado 2011	Used myo-inositol as a treatment intervention in women diagnosed with gestational diabetes, not preventative.
Matarrelli 2013	Used myo-inositol as a treatment intervention in women diagnosed with gestational diabetes, not a preventative.

Characteristics of ongoing studies *[ordered by study ID]*

Farren 2013

Trial name or title	A randomised controlled trial to investigate the role of the food supplement inositol in the general health of those at risk of developing gestational diabetes mellitus.
Methods	Single-blind randomised controlled trial.
Participants	Any woman aged over 18 booking before 14 weeks' gestation with a first-degree relative with diabetes mellitus.
Interventions	2 intervention arms: myo-inositol 4 g + 400 mcg folic acid; per day; myo-inositol 550 mg + 13.8 mg D-chiro-inositol + 400 mcg folic acid per day. Placebo group: folic acid 400 mcg per day.
Outcomes	Development of gestational diabetes mellitus, measured at 26 weeks' gestation.
Starting date	01/11/2013.
Contact information	Dr Maria Farren, mariafarren1983@gmail.com
Notes	Expected completion 01/06/2015. Alternative primary investigator: Sean Daly ISRCTN92466608

mcg: micrograms

DATA AND ANALYSES

Comparison 1. Myo-inositol versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gestational diabetes mellitus	3	502	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.29, 0.64]
2 Fasting OGTT	3	502	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.12]
3 One hour OGTT	3	502	Mean Difference (IV, Fixed, 95% CI)	-0.68 [1.00, -0.37]
4 Two hour OGTT	3	502	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.07, -0.43]
5 Hypertensive disorders of pregnancy	2	398	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.02, 8.41]
6 Caesarean section	2	398	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.19]
7 Weight gain during pregnancy	2	411	Mean Difference (IV, Random, 95% CI)	0.64 [-0.41, 1.70]
8 Relevant biomarker changes associated with the intervention	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Total cholesterol	1	48	Mean Difference (IV, Fixed, 95% CI)	-47.29 [-52.87, -41.71]
8.2 Low density lipoprotein	1	48	Mean Difference (IV, Fixed, 95% CI)	-33.50 [-39.71, -27.29]
8.3 High density lipoprotein	1	48	Mean Difference (IV, Fixed, 95% CI)	-13.79 [-18.91, -8.67]
8.4 Triglycerides	1	48	Mean Difference (IV, Fixed, 95% CI)	-39.33 [-44.00, -34.66]
9 Adverse effects of intervention	2	245	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Supplementary insulin	2	398	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.11, 2.09]
11 Gestational age at birth	2	398	Mean Difference (IV, Random, 95% CI)	5.50 [-7.24, 18.24]
12 Preterm birth (less than 37 weeks' gestation)	2	398	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.17, 1.14]
13 Macrosomia	2	398	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.02, 6.37]
14 Birthweight	2	398	Mean Difference (IV, Random, 95% CI)	-60.47 [-265.21, 144.26]
15 Shoulder dystocia	2	398	Risk Ratio (M-H, Random, 95% CI)	2.33 [0.12, 44.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Respiratory distress syndrome	1	197	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.06, 15.60]
17 Neonatal hypoglycaemia	2	398	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.01, 8.66]

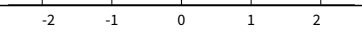
Analysis 1.1. Comparison 1 Myo-inositol versus control, Outcome 1 Gestational diabetes mellitus.

Study or subgroup	Myo-inositol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Anna 2013	6/99	15/98		22.36%	0.4[0.16,0.98]
D'Anna 2015	15/107	36/107		53.39%	0.42[0.24,0.71]
Facchinetti 2013	6/31	24/60		24.25%	0.48[0.22,1.06]
Total (95% CI)	**237**	**265**		**100%**	**0.43[0.29,0.64]**
Total events: 27 (Myo-inositol), 75 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.13, df=2(P=0.94); I^2=0%					
Test for overall effect: Z=4.16(P<0.0001)					

Favours myo-inositol — Favours control

Analysis 1.2. Comparison 1 Myo-inositol versus control, Outcome 2 Fasting OGTT.

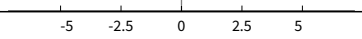
Study or subgroup	Myo-inositol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
D'Anna 2013	99	4.3 (0.4)	98	4.5 (0.5)		43%	-0.2[-0.33,-0.07]
D'Anna 2015	107	4.5 (0.4)	107	4.7 (0.6)		36.87%	-0.2[-0.34,-0.06]
Facchinetti 2013	31	4.5 (0.3)	60	4.7 (0.6)		20.13%	-0.2[-0.38,-0.02]
Total ***	**237**		**265**			**100%**	**-0.2[-0.28,-0.12]**
Heterogeneity: Tau^2=0; Chi^2=0, df=2(P=1); I^2=0%							
Test for overall effect: Z=4.72(P<0.0001)							



Favours myo-inositol — Favours placebo

Analysis 1.3. Comparison 1 Myo-inositol versus control, Outcome 3 One hour OGTT.

Study or subgroup	Myo-inositol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
D'Anna 2013	99	6.8 (1.7)	98	7.4 (1.7)		43.93%	-0.6[-1.07,-0.13]
D'Anna 2015	107	7.1 (1.9)	107	7.9 (1.7)		42.44%	-0.8[-1.28,-0.32]
Facchinetti 2013	31	7.5 (2)	60	8.1 (1.9)		13.63%	-0.6[-1.45,0.25]
Total ***	**237**		**265**			**100%**	**-0.68[-1,-0.37]**
Heterogeneity: Tau^2=0; Chi^2=0.38, df=2(P=0.83); I^2=0%							
Test for overall effect: Z=4.27(P<0.0001)							



Favours myo-inositol — Favours placebo

Analysis 1.4. Comparison 1 Myo-inositol versus control, Outcome 4 Two hour OGTT.

Study or subgroup	Myo-inositol N	Myo-inositol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
D'Anna 2013	99	5.6 (1.2)	98	6.1 (1.5)		41.14%	-0.5[-0.88,-0.12]
D'Anna 2015	107	5.8 (1.4)	107	6.8 (1.7)		36.79%	-1[-1.42,-0.58]
Facchinetti 2013	31	6.5 (1.2)	60	7.3 (1.7)		22.07%	-0.8[-1.4,-0.2]
Total ***	**237**		**265**			**100%**	**-0.75[-1.07,-0.43]**
Heterogeneity: Tau^2=0.03; Chi^2=3.07, df=2(P=0.22); I^2=34.75%							
Test for overall effect: Z=4.55(P<0.0001)							

Analysis 1.5. Comparison 1 Myo-inositol versus control, Outcome 5 Hypertensive disorders of pregnancy.

Study or subgroup	Myo-inositol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
D'Anna 2013	3/99	2/98		57.02%	1.48[0.25,8.69]
D'Anna 2015	0/97	6/104		42.98%	0.08[0,1.44]
Total (95% CI)	**196**	**202**		**100%**	**0.43[0.02,8.41]**
Total events: 3 (Myo-inositol), 8 (Control)					
Heterogeneity: Tau^2=3.23; Chi^2=3.19, df=1(P=0.07); I^2=68.69%					
Test for overall effect: Z=0.56(P=0.58)					

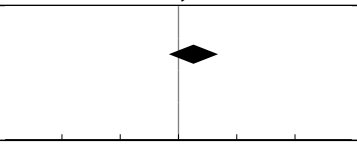
Analysis 1.6. Comparison 1 Myo-inositol versus control, Outcome 6 Caesarean section.

Study or subgroup	Myo-inositol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Anna 2013	42/99	43/98		48.26%	0.97[0.7,1.33]
D'Anna 2015	42/97	48/104		51.74%	0.94[0.69,1.28]
Total (95% CI)	**196**	**202**		**100%**	**0.95[0.76,1.19]**
Total events: 84 (Myo-inositol), 91 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=0.43(P=0.66)					

Analysis 1.7. Comparison 1 Myo-inositol versus control, Outcome 7 Weight gain during pregnancy.

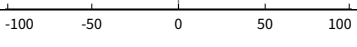
Study or subgroup	Myo-inositol N	Myo-inositol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
D'Anna 2013	99	7.2 (2.6)	98	7 (3)		59.73%	0.2[-0.58,0.98]
D'Anna 2015	107	5.9 (4.7)	107	4.6 (4.5)		40.27%	1.3[0.07,2.53]

Study or subgroup	Myo-inositol N	Myo-inositol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Total ***	**206**		**205**			**100%**	**0.64[-0.41,1.7]**
Heterogeneity: Tau²=0.33; Chi²=2.18, df=1(P=0.14); I²=54.06%							
Test for overall effect: Z=1.19(P=0.23)							



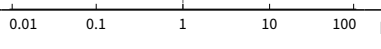
Analysis 1.8. Comparison 1 Myo-inositol versus control, Outcome 8 Relevant biomarker changes associated with the intervention.

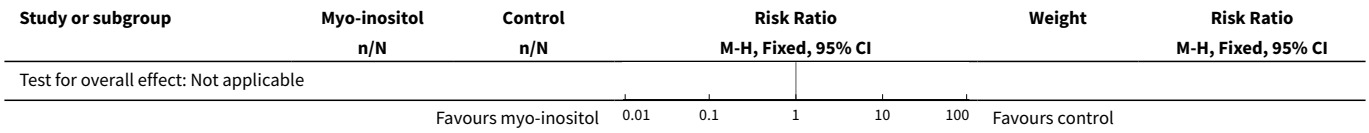
Study or subgroup	Myo-inositol N	Myo-inositol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.8.1 Total cholesterol							
Malvasi 2014	24	185.4 (10.8)	24	232.7 (8.8)		100%	-47.29[-52.87,-41.71]
Subtotal ***	**24**		**24**			**100%**	**-47.29[-52.87,-41.71]**
Heterogeneity: Not applicable							
Test for overall effect: Z=16.61(P<0.0001)							
1.8.2 Low density lipoprotein							
Malvasi 2014	24	124.8 (9.9)	24	158.3 (12)		100%	-33.5[-39.71,-27.29]
Subtotal ***	**24**		**24**			**100%**	**-33.5[-39.71,-27.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=10.57(P<0.0001)							
1.8.3 High density lipoprotein							
Malvasi 2014	24	60.5 (10.3)	24	74.3 (7.7)		100%	-13.79[-18.91,-8.67]
Subtotal ***	**24**		**24**			**100%**	**-13.79[-18.91,-8.67]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.27(P<0.0001)							
1.8.4 Triglycerides							
Malvasi 2014	24	136.4 (7.6)	24	175.7 (8.9)		100%	-39.33[-44,-34.66]
Subtotal ***	**24**		**24**			**100%**	**-39.33[-44,-34.66]**
Heterogeneity: Not applicable							
Test for overall effect: Z=16.49(P<0.0001)							
Test for subgroup differences: Chi²=86.24, df=1 (P<0.0001), I²=96.52%							



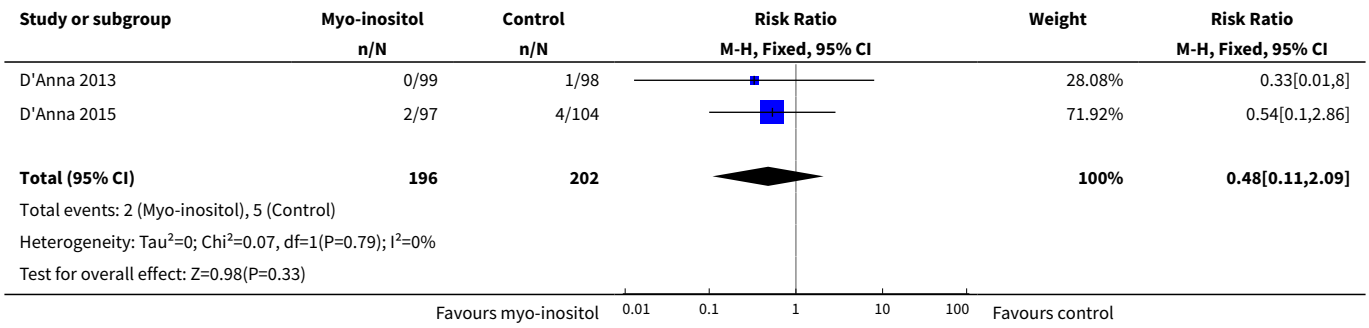
Analysis 1.9. Comparison 1 Myo-inositol versus control, Outcome 9 Adverse effects of intervention.

Study or subgroup	Myo-inositol n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
D'Anna 2013	0/99	0/98			Not estimable
Malvasi 2014	0/24	0/24			Not estimable
Total (95% CI)	**123**	**122**			**Not estimable**
Total events: 0 (Myo-inositol), 0 (Control)					
Heterogeneity: Not applicable					

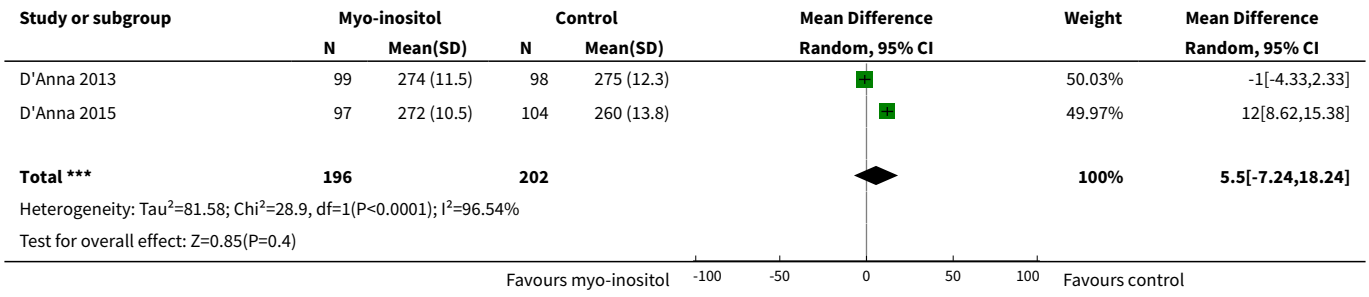




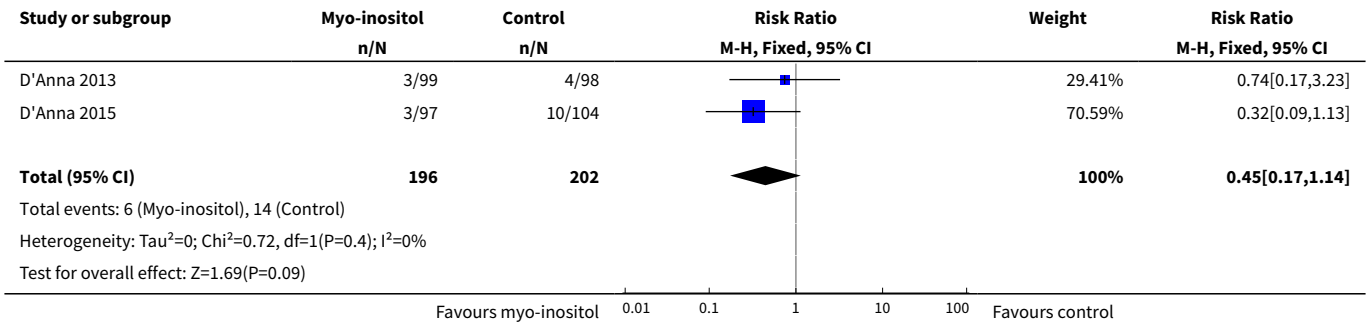
Analysis 1.10. Comparison 1 Myo-inositol versus control, Outcome 10 Supplementary insulin.



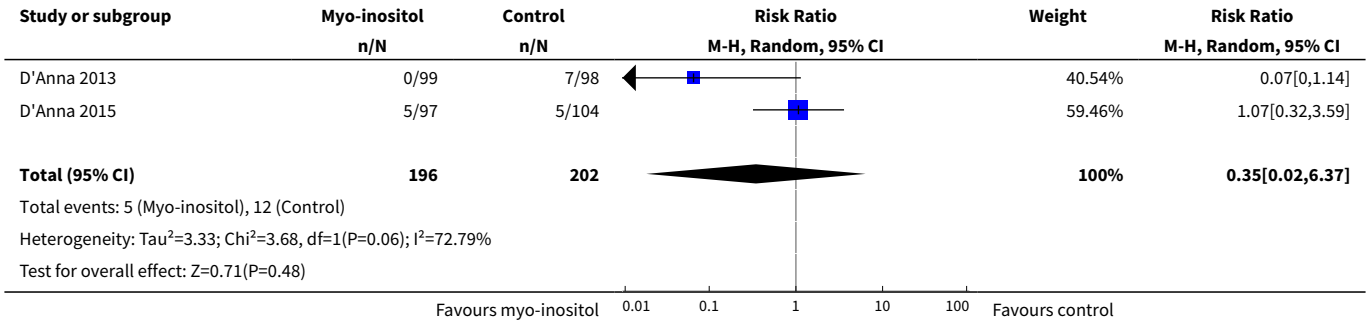
Analysis 1.11. Comparison 1 Myo-inositol versus control, Outcome 11 Gestational age at birth.



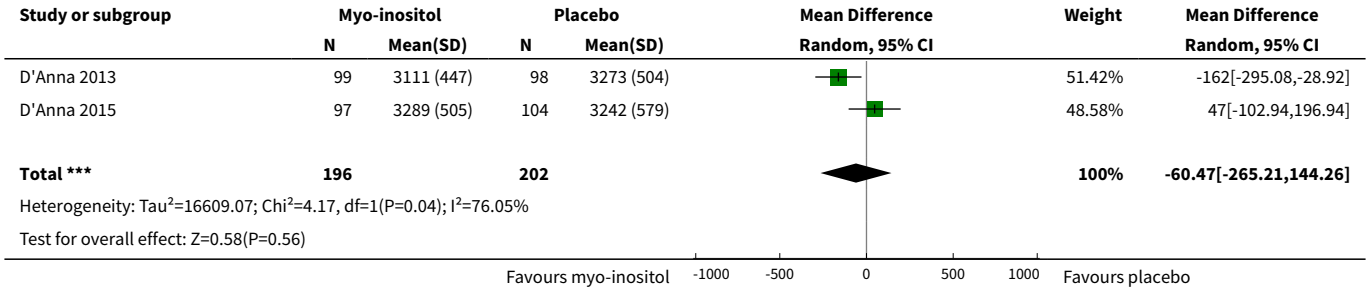
Analysis 1.12. Comparison 1 Myo-inositol versus control, Outcome 12 Preterm birth (less than 37 weeks' gestation).



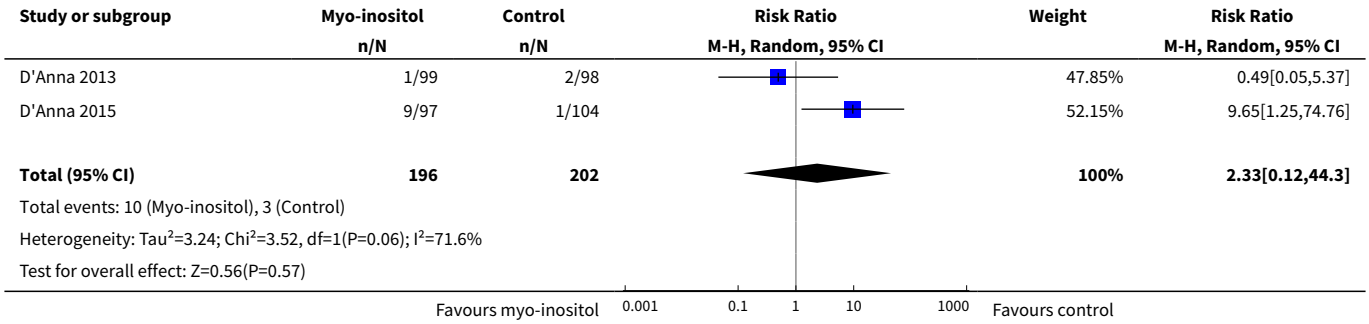
Analysis 1.13. Comparison 1 Myo-inositol versus control, Outcome 13 Macrosomia.



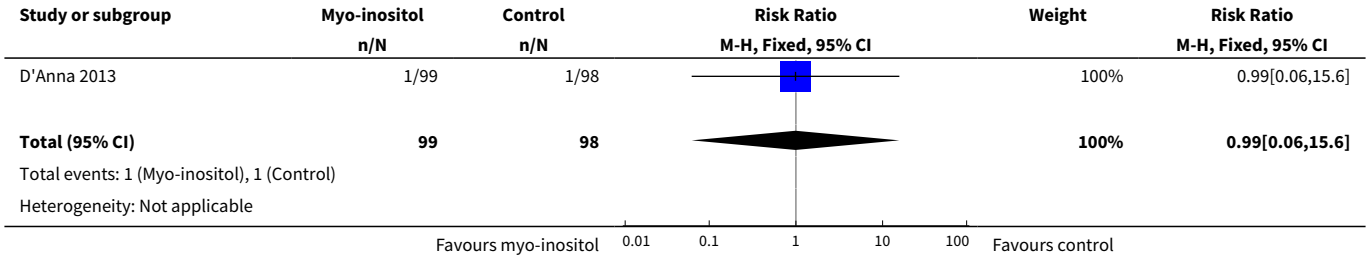
Analysis 1.14. Comparison 1 Myo-inositol versus control, Outcome 14 Birthweight.

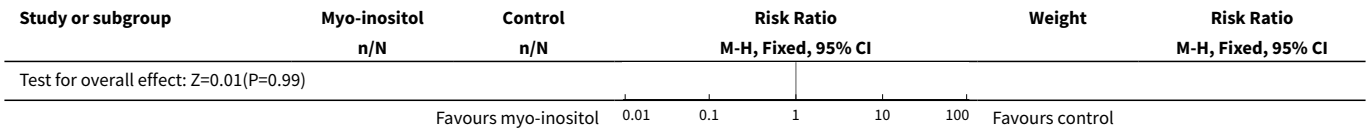


Analysis 1.15. Comparison 1 Myo-inositol versus control, Outcome 15 Shoulder dystocia.

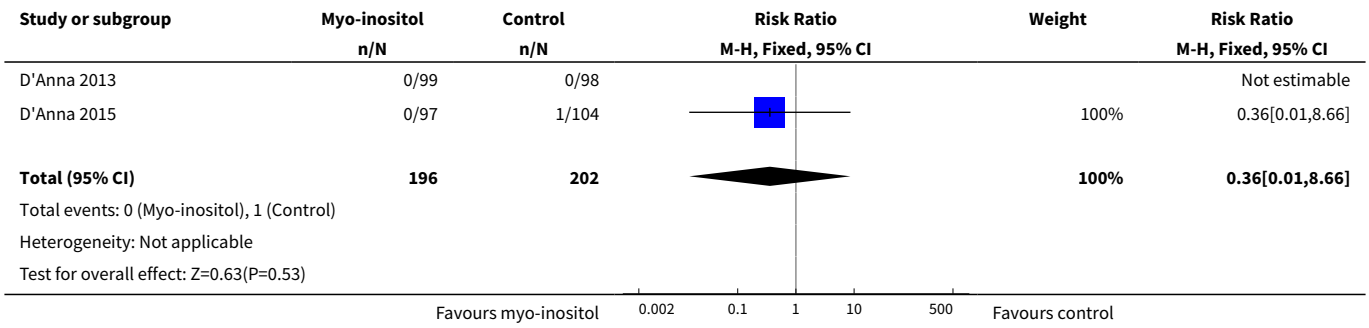


Analysis 1.16. Comparison 1 Myo-inositol versus control, Outcome 16 Respiratory distress syndrome.





Analysis 1.17. Comparison 1 Myo-inositol versus control, Outcome 17 Neonatal hypoglycaemia.



APPENDICES

Appendix 1. Search terms

ClinicalTrials.gov and WHO ICTRP

gestational diabetes AND myoinositol

gestational diabetes AND myo-inositol

gestational diabetes AND myo inositol

gestational diabetes AND inositol)

gdm AND myoinositol

gdm AND myo-inositol

gdm AND myo inositol

gdm AND inositol

CONTRIBUTIONS OF AUTHORS

Tineke Crawford is guarantor for this review.

Tineke Crawford screened search results, retrieved relevant papers, screened retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, wrote to authors of papers for additional information, entered data into RevMan, analysed and interpreted data, wrote the first draft of the review, incorporated feedback into subsequent versions of the review.

Julie Brown conceived the review, screened retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, checked data in RevMan, analysed and interpreted data, providing a methodological perspective, contributed to subsequent versions of the review.

Jane Alsweiler appraised quality of papers, extracted data from papers, analysed and interpreted data, providing a neonatal clinical perspective, and contributed to subsequent versions of the review.

Caroline Crowther provided a maternal clinical and methodological perspective.

DECLARATIONS OF INTEREST

Professor Caroline Crowther, Dr Julie Brown and Dr Jane Aslweiler are investigators on a planned trial of myo-inositol supplements in pregnancy for the prevention of gestational diabetes. If this trial is eligible for inclusion in this review, Professor Caroline Crowher, Dr Julie Brown and Dr Jane Aslweiler will not be involved in any aspect of data extraction or risk of bias relating to this trial. Tineke Crawford and another researcher not involved in the trial will deal with the handling of these data.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- The Cochrane Pregnancy and Childbirth Review Group editorial team, Liverpool, UK.
- The Australasian Satellite of the Cochrane Pregnancy and Childbirth Review Group (Funded by NHMRC), Adelaide, Australia.

  (incorporating the New Zealand branch)
- The Liggins Institute, The University of Auckland, New Zealand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are some differences between our published protocol (Brown 2015) and the full review.

The title was listed as *Myo-inositol for preventing gestational diabetes* in our published protocol but we have edited this to *Antenatal dietary supplementation with myo-inositol in women during pregnancy for preventing gestational diabetes* in order to allow more clarity around the intervention, population and outcome.

Methods/Criteria for considering studies for this review

Types of interventions: we have expanded this section to include myo-inositol in a combination preparation; this is also reflected in our list of planned subgroup analyses.

Types of participants: we have clarified that participants will be pregnant women rather than pregnant women at risk of gestational diabetes mellitus (GDM).

We have incorporated the use of GRADE to assess the quality of the body of evidence and have included 'Summary of findings' tables; this was not pre-specified in our published protocol.

We have reported on the outcome 'need for supplementary insulin therapy' - whilst this is not listed in our methods/outcomes section (and was not pre-specified in our published protocol), we report on this outcome for interest.

Following a consultative process with Professor Caroline Crowther, Dr Julie Brown, Dr Philippa Middleton, Emily Bain and Tineke Crawford, a core set of primary and secondary outcomes for GDM systematic reviews and core outcomes for GRADE assessment for GDM systematic reviews were drawn up. This has resulted in a number of changes detailed below. These core outcomes were agreed upon after this review had been submitted for peer review.

Additionally, as this is a review on the use of a dietary supplement as an intervention, adverse effects of the intervention has been added as an outcome.

Previous maternal primary outcomes listed in protocol

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

Updated maternal primary outcomes used in review

1. Gestational diabetes mellitus (GDM)
2. Hypertensive disorders of pregnancy (including pre-eclampsia, eclampsia, pregnancy-induced hypertension)

Previous neonatal primary outcomes listed in protocol

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)

Updated neonatal primary outcomes used in review

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)

Previous maternal secondary outcomes listed in protocol

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. Perineal trauma
10. Weight gain during pregnancy
11. Adiponectin levels
12. Gestational age at screening for GDM
13. Postpartum haemorrhage
14. Postpartum infection
15. Placental abruption
16. Polyhydramnios
17. Compliance with treatment
18. Breastfeeding at discharge, six weeks' postpartum
19. Women’s sense of well-being and quality of life (as defined in individual trials)
20. Women’s view of intervention

Updated maternal secondary outcomes used in review

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

Long-term maternal outcomes

1. Postnatal depression
2. Postnatal weight retention or return to pre-pregnancy weight
3. Body mass index (BMI)
4. Gestational diabetes mellitus in a subsequent pregnancy

5. Type I diabetes mellitus
6. Type II diabetes mellitus
7. Impaired glucose tolerance
8. Cardiovascular health (as defined by trialists, including blood pressure (BP), hypertension, cardiovascular disease, metabolic syndrome)

Previous neonatal secondary outcomes listed in protocol

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 adiposity (as defined in individual trials)
17. Neonatal glucose concentration
18. Infant mortality (fetal, neonatal, perinatal)

Updated secondary outcomes used in review

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
13. Shoulder dystocia
14. Bone fracture
15. Nerve palsy
16. Respiratory distress syndrome
17. Hypoglycaemia (variously defined)
18. Hyperbilirubinaemia

Previous childhood outcomes listed in protocol

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

Updated childhood outcomes used in review

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 I diabetes mellitus
7. Type II diabetes mellitus
8. Impaired glucose tolerance
9. Dyslipidaemia or metabolic syndrome
10. Neurodisability
11. Educational achievement

Previous adulthood outcomes listed in protocol

1. Weight
2. Height
3. BMI
4. Adiposity (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

Updated adulthood outcomes used in review

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

Previous health services cost outcomes listed in protocol

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

Updated health services cost outcomes used in review

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
9. Cost of maternal care
10. Cost of offspring care

Previous GRADE outcomes listed in protocol

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 child/adult

Updated GRADE outcomes used in review

Maternal

1. Diagnosis of GDM
2. Gestational weight gain
3. Hypertensive disorders of pregnancy (including pre-eclampsia, eclampsia, pregnancy-induced hypertension)
4. Caesarean Section
5. Perineal trauma
6. Postnatal depression
7. Development of subsequent type II 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

INDEX TERMS

Medical Subject Headings (MeSH)

*Prenatal Care; Diabetes, Gestational [epidemiology] [*prevention & control]; Incidence; Inositol [adverse effects] [chemistry] [*therapeutic use]; Isomerism; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy