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Review Article

The Efficacy and Safety of Myo-inositol Supplementation for the Prevention of Gestational Diabetes Mellitus in Overweight and Obese Pregnant Women: A Systematic Review and Meta-Analysis

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Abstract

Background. Myo-inositol has emerged as one of the preventive therapies for the development of gestational diabetes mellitus in at-risk populations. This systematic review and meta-analysis was conducted to determine the efficacy and safety of myo-inositol in decreasing the incidence of gestational diabetes in overweight and obese pregnant women.

Methodology. This meta-analysis was conducted using the standard Cochrane methodology and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines. Inclusion criteria were randomized controlled trials (RCTs) that enrolled overweight and obese pregnant women and used myo-inositol supplementation. The primary outcome was the incidence of gestational diabetes mellitus at 24-28 weeks. Secondary outcomes included cesarean section rate, the incidence of pregnancy-induced hypertension, macrosomia and preterm delivery. Risk ratios (RRs) and 95% confidence intervals (CIs) were used for dichotomous data.

Results. Six RCTs were included. Compared to standard micronutrient supplementation, standard dose of myo-inositol (4 g) may reduce the incidence of GDM (RR 0.54; CI [0.30, 0.96]; n = 887 women), but the certainty of evidence is low to very low. With low-dose myo-inositol however, evidence is uncertain about its benefit on the incidence of gestational diabetes mellitus in overweight and obese women with RR 0.71; CI [0.14, 3.50]. No adverse effects were noted. For the secondary outcomes, standard dose myo-inositol appears to reduce the incidence of pregnancy-induced hypertension and preterm delivery, but the certainty of evidence is low to very low.

Conclusion. Current evidence is uncertain on the potential benefit of myo-inositol supplementation in overweight and obese pregnant women. While studies show that 4 g myo-inositol per day may decrease the incidence of GDM, pregnancy-induced hypertension and pre-term birth with no associated risk of serious adverse events, the certainty of evidence is low to very low. Future high-quality trials may provide more compelling evidence to support practice recommendations.

Key words: gestational diabetes, obesity, inositol phosphates

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as any level of glucose intolerance diagnosed for the first time during pregnancy.[1] Pregnancies complicated by GDM are at risk of both short-term and long-term consequences. Adverse fetal outcomes include large for gestational age infants and stillbirths,[2,3] while adverse maternal outcomes include the development of pre-eclampsia and gestational hypertension.[2,4]

Being overweight and obese increases the risk of gestational diabetes mellitus.[2,3] Adverse neonatal outcomes such as macrosomia have also been associated with elevated pre-pregnancy body mass index (BMI).[4] In Asians, a BMI ≥25 kg/m^2 was associated with an odds ratio (OR) of 3.27 for the development of GDM.[5]

Myo-inositol

Myo-inositol is an insulin-sensitizing agent naturally found in fruits, nuts and beans. Upon binding with its receptor (IR), insulin induces IRS-1 recruitment and activation. One of the principal IR/IRS targets, PI3K, then generates Phosphatidylinositol to activate PDK1 and subsequently PKB/Akt. These actions are involved in GLUT4 translocation and glycogen synthesis. In essence, myo-inositol acts as a secondary messenger that facilitates the transfer of glucose into the cell.[6]

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At the molecular level, insulin resistance is associated with a failure of insulin signaling, resulting in inadequate plasma membrane translocation of glucose transporter 4 (GLUT4). The increase in insulin sensitivity in patients who take myo-inositol may be an important intervention to prevent the development of GDM in high-risk women.[7]

Myo-inositol is a relatively cheap and widely available supplement that may be an effective strategy for GDM prevention in overweight/obese pregnant women. While studies have looked at the effect of myo-inositol supplementation in overweight and obese pregnant women, the sample sizes were not powered to detect differences in outcomes between groups.

OBJECTIVES

This review assessed if the supplementation of myo-inositol among pregnant women with a BMI ≥25 kg/m^2 is safe and effective in preventing GDM and other adverse maternal and neonatal outcomes. Specifically, we answered the following research question: Among pregnant women with BMI >25 kg/m^2, does supplementation with myo-inositol decrease the incidence of GDM, pregnancy-induced hypertension, cesarean section, preterm delivery and macrosomia?

METHODOLOGY

All published and unpublished randomized controlled trials assessing the effects of myo-inositol for the prevention of gestational diabetes mellitus among obese and overweight pregnant women were included. Case reports, observational studies and non-randomized trials were excluded.

We included trials that enrolled pregnant women classified as overweight or obese or whose body mass index is greater than or equal to 25 kg/m^2. Women already diagnosed with gestational diabetes mellitus and pregestational diabetes were excluded.

The intervention investigated was myo-inositol administered at any dose, alone or in combination, to prevent GDM and other adverse perinatal outcomes. Studies that compared the intervention with standard micronutrient supplementation alone or in combination were included.

The primary efficacy outcome was the incidence of Gestational Diabetes Mellitus (as defined by the IADPS Criteria). The primary safety outcome was the incidence of adverse effects. Secondary outcomes included incidence of pregnancy-induced hypertension and Cesarean section. For neonatal outcomes, the incidence of macrosomia and preterm birth were included.

Search terms included inositol, myo-inositol, gestational diabetes mellitus, GDM, obese and overweight. Randomized control trial was used as a filter. We searched the following databases from inception until March 3, 2022: The Cochrane Library, MEDLINE, Scopus, Google Scholar, MedRXIV, and Research Square. We also searched databases of unpublished, planned, and ongoing trials, including ClinicalTrials.gov (http://clinicaltrials.gov/), the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/), and the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (https://trialsearch.who.int/).

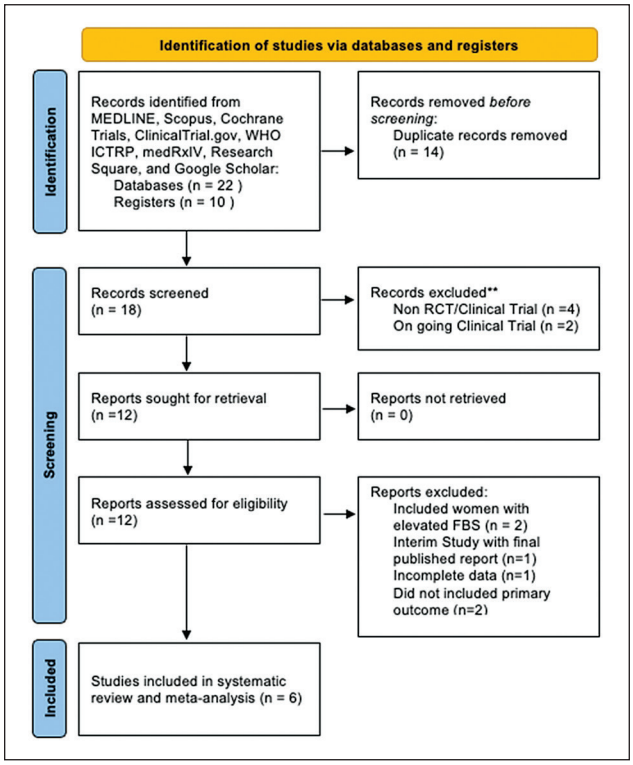

Figure 1. PRISMA Flowchart of Study Selection.

Data collection and analysis

Two review authors (HC, PF) independently scanned the title and abstract of every record retrieved to determine which studies should be assessed further. All potentially relevant articles were retrieved as full text and reviewed independently. Please refer to the adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of study selection (Figure 1).

Data extraction and management

Data were extracted by the two review authors (HC, PF) using a data extraction form based on the Cochrane Pregnancy and Childbirth Group's data extraction form. Any disagreements were resolved by discussion. Review Manager (RevMan v 5.4.1) was used to encode all data. All data was encoded in Review Manager.

Assessment of risk of bias in included studies

Two review authors (HC, PF) assessed the risk of bias in each included study independently. Disagreements were resolved by discussion. We used the Cochrane

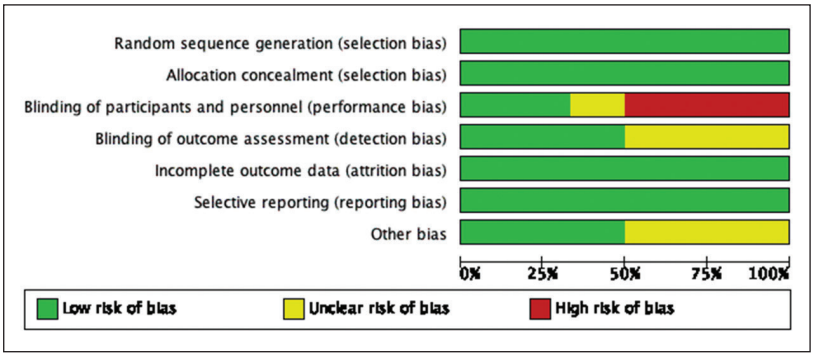

Figure 2. Risk of bias graph: review author's judgement about each risk of bias item presented as percentage across all included studies.

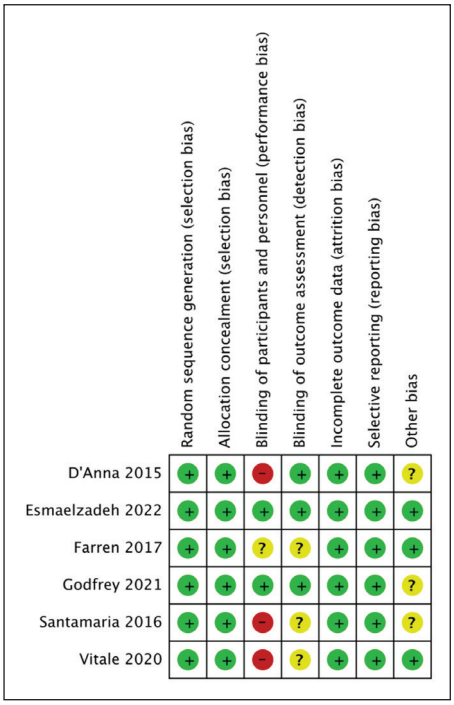

Figure 3. Risk of bias summary: Review authors' judgements about each risk of bias item for each included study.

Collaboration tool for the assessment of the risk of bias. We judged the risk of bias as 'low risk,' 'high risk' or 'unclear risk' and evaluated individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions. The risk of bias within and across studies was presented graphically using RevMan (Figures 2 and 3).

Measures of treatment effect

Dichotomous data were expressed as risk ratios (RRs) with 95% confidence intervals (CIs).

Assessment of heterogeneity

Heterogeneity was identified by visually examining the forest plot and using a standard Chi-test^2 with a significance level of $\alpha = 0.05$. The I^2 statistic was used to assess the impact of heterogeneity on the meta-analysis; an I^2 statistic of 50% or more indicates a considerable level of inconsistency. Study results were not reported as pooled effects because of substantial clinical and methodological heterogeneity.

Data synthesis

Because of substantial clinical and methodological heterogeneity, a random-effects model was used to summarize data.

Subgroup analysis and investigation of heterogeneity

The authors did a subgroup analysis of standard dose (4 g) vs. low dose (≤2 g) of myo-inositol. Certainty of evidence was graded using GradePro, and discrepancies were settled through consensus.

RESULTS

Search strategy

We identified 32 reports; fourteen were duplicates, and six were excluded at the title and abstract stage. Of the twelve studies assessed for eligibility, only six were included. The study selection schematic diagram is shown in Figure 1.

Study characteristics

We included six published randomized controlled trials: D'Anna 2015, Santamaria 2016, Farren 2017, Vitale 2020, Godfrey 2021 and Esmaelzadeh 2022.[8–13] The baseline characteristics of the included studies are summarized in Table 1.

Duration of treatment with myo-inositol varied between studies. Most of the studies started upon recruitment at 10-16 weeks of gestation (AOG) and continued throughout the pregnancy.[8-11] In one study, it was given before conception until delivery.[12] In another study, myo-inositol was started upon recruitment at 12-14 weeks AOG until the 24th week of gestation.[13]

Effects of interventions

Primary outcomes

Incidence of gestational diabetes mellitus

For the mother, myo-inositol supplementation was associated with a reduction in the incidence of GDM in a

Table 1. General characteristics of the studies

References	Country and time of realization	Participants and main inclusion criteria	Intervention and timing	Intervention group	Control Group	Maternal health outcomes	Feto-neonatal health outcomes	Metabolic outcomes
D'Anna et al. 2015	Italy January 2011 - April 2014	220 obese pregnant women from Italy Eligibility criteria: pre-pregnancy BMI ≥30 kg/m^2, singleton gestation	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	Group A: (n = 97) Age: 30.09 (18-44) BMI: 33.8 (30-46.9)	Group B: (n = 104) Age: 31.7 (19-43) BMI: 33.8 (30-46) 400 mg folic acid daily (200 mg folic acid orally twice a day), and nutritional and lifestyle counselling (n = 110)	GDM incidence Gestational hypertension Weight increase Adverse events CS rate	Preterm delivery Macrosomia Birth weight GA at birth Neonatal hypoglycemia NICU admission	OGTT – FBS, 1st hr, and 2nd hr
Santamaria et al. 2016	Italy Beginning of 2012 (36 months duration)	Overweight pregnant women Inclusion criteria were: (1) pre-pregnancy BMI 425 and 530 kg/m^2; (2) first trimester fasting plasma glucose <126 mg/dl and/or random glycemia <200 mg/dl; (3) single pregnancy; and (4) Caucasian ethnicity.	Treatment arm: 2000 mg myo-inositol + 200 mcg folic acid 2x/day Duration of myo-inositol supplementation: from trial entry until the end of pregnancy	Group A: (n = 95) Age: 32.1 (± 4.8) BMI: 26.9 (± 1.3)	Group B: (n = 102) Age: 32.7 (± 5.3) BMI: 27.1 (± 1.3) 400 mcg folic acid per day	GDM incidence Gestational hypertension Weight increase Adverse events CS rate	Preterm delivery Macrosomia Birth weight GA at birth Neonatal hypoglycemia NICU admission	OGTT – FBS, 1st hr, and 2nd hr
Farren et al. 2017	Ireland January 2014 - January 2016	240 Pregnant women with a family history of DM recruited at their first visit between 10 and 16 weeks' gestation. Eligibility Criteria: Women with a family history in a first-degree relative of diabetes, either type 1 or type 2, were eligible for inclusion.	1,100 mg myo-inositol + 27.6 mg D-chiro inositol + 400 mcg folic acid Duration: from enrollment throughout pregnancy	Group A: (n = 120) Age: 31.1 ± 5.1 BMI: 26 ± 5.3	Group B: (n = 120) Age: 31.5 ± 5 BMI: 26.2 ± 5.5 400 mcg of folic acid per day	GD incidence Gestational hypertension Adverse events CS rate	Preterm delivery Shoulder dystocia Macrosomia Birthweight GA at birth Neonatal hypoglycemia NICU admission	OGTT

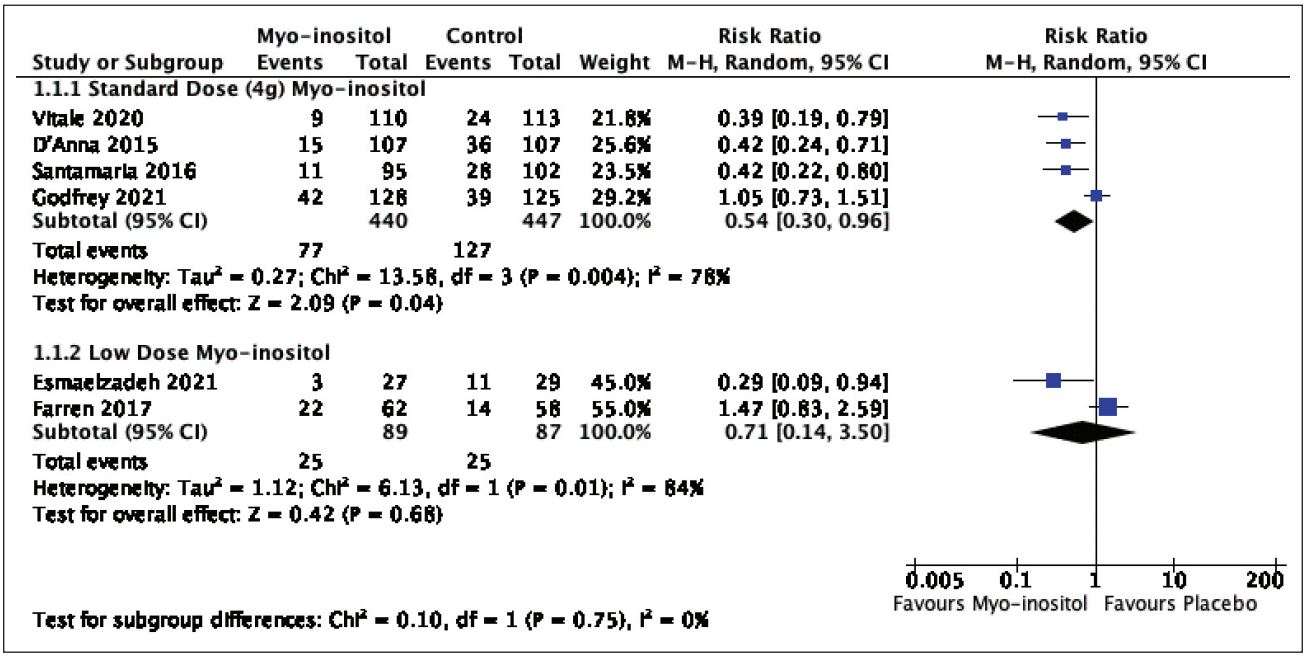

Figure 4. Forest plot of the effect of myo-inositol on the incidence of gestational diabetes mellitus in overweight and obese pregnant women.

Table 1. General characteristics of the studies *(continued)*

References	Country and time of realization	Participants and main inclusion criteria	Intervention and timing	Intervention group	Control Group	Maternal health outcomes	Feto-neonatal health outcomes	Metabolic outcomes
Godfrey et al. 2021	Randomized, double-blind, controlled trial Multisite: New Zealand, UK, and Singapore	Women 18-38 years old planning conception Eligibitlity Criteria: Aged 18–38 years, were planning to conceive within 6 months, and had future maternity care at the recruiting centers *included a sub-analysis of overweight and obese pregnant women using ethnic cut-offs: BMI >23 kg/m^2 for Asians including Chinese, Indians, Pakistani, Bangladeshi, Malay, mixed Asian; >25 kg/m^2 for non-Asians including White Caucasian, Polynesian, Black, mixed Asian-non-Asian	Intervention: additionally included myo-inositol 4 g/day, vitamin D 10 µg/day, riboflavin 1.8 mg/day, vitamin B6 2.6 mg/day, vitamin B12 5.2 µg/day, zinc 10 mg/day, and probiotics (Lactobacillus rhamnosus NCC 4007 [CGMCC 1.3724] and Bifidobacterium animalis subspecies lactis NCC 2818 [CNCM I-3446] Duration: from pre-conception throughout pregnancy	Group A: 128 No subgroup data regarding average age and BMI	Group B: 125 No subgroup data regarding average age and BMI Folic acid 400 µg/day, iron 12 mg/day, calcium 150 mg/day, iodine 150 µg/day, and β-carotene 720 µg/day	GDM incidence Adverse effects		OGTT
Vitale et al. 2020	Italy Beginning of 2016 and lasted 2 years	Overweight pregnant women Eligibility Criteria: pre-pregnancy BMI >25 and <30 kg/m^2, first-trimester fasting plasma glucose 126 mg/dl and/or random glycaemia <200 mg/dl, single pregnancy, and Caucasian ethnicity	Intervention: 2000 mg myo-inositol + 200 mcg folic acid 2x/day Intervention given from enrollment until 3 weeks postpartum	Group A: N = 110 Age: 27.18 ± 6.03 BMI: 27.00 ± 1.49	Group B: N = 113 Age: 27.95 ± 4.90 BMI: 26.68 ± 1.56 Control: Folic acid 200 mcg 2x/day	Incidence of GDM CS rate pregnancy-induced hypertension	macrosomia preterm delivery	change in lipid metabolism
Esmaelzadeh 2022	Iran From April 2018 - February 2020	Overweight pregnant women 12-14 weeks AOG Eligibility Criteria: Overweight pregnant women (BMI >25 kg/m^2)	Intervention: 2000 mg myo-inositol + 200 mcg folic acid a day Given from enrollment until 24 weeks AOG	Group A: n = 27 Age: 27.8 ± 4.2 BMI: 27.3 ± 1.8	Group B: n = 29 Age: 29.3 ± 4.4 BMI: 26.9 ± 1.9	GDM incidence Insulin therapy Weight gain Gestational hypertension CS rate	Preterm delivery Fetal macrosomia Shoulder dystocia NICU admissions RDS	OGTT Fasting insulin HOMA IR Total cholesterol trigyceride

dose-dependent manner in overweight and obese women. As seen in Figure 4, using the standard dose of 4 g, there appears to be a reduction in GDM (risk ratio 0.54, CI [0.30, 0.96]; n = 887). Using low-dose myo-inositol, the risk ratio is 0.71 with CI between [0.14, 3.50], crossing the line of no benefit. Thus, the evidence shows uncertain benefits of low-dose myo-inositol on the incidence of gestational diabetes mellitus in overweight and obese women.

There was significant heterogeneity in the studies, with I^2 of 78% and 82% for standard dose myo-inositol and low-dose myo-inositol, respectively. For standard dose myo-inositol, the heterogeneity is most likely due to differences in ethnicity, with Godfrey including mixed races, while D'Anna, Santamaria and Vitale had a predominantly Italian population.[8,9,11,12] The presence of other micronutrients with myo-inositol is also a notable difference between Godfrey and the studies done in Italy which may also explain the significant heterogeneity. For the low dose myo-inositol, I^2 was 82%; this may be explained by the difference in the study population, the duration of intervention and the addition of D-chiro-inositol.[10]

Using GRADEpro Guideline Development Tool, standard dose (4 g) myo-inositol may decrease the risk of gestational diabetes mellitus in overweight and obese pregnant women, while low dose myo-inositol has no effect on the incidence of GDM. Certainty of evidence is very low because of a high risk of performance bias, inconsistency and imprecision. The risk of GDM in women who received 4g myo-inositol is 15.3%, while for women in the control group, the risk is 28.4%.

Adverse events

All studies looked into the rate of adverse events with the intake of myo-inositol. In all studies, no significant adverse events were observed for both treatment and placebo groups.

Secondary outcomes

Incidence of cesarean section

Three trials reported on cesarean section rate with the intake of myo-inositol in obese and overweight pregnant women.[8,9,13] For standard dose myo-inositol, RR was 0.89

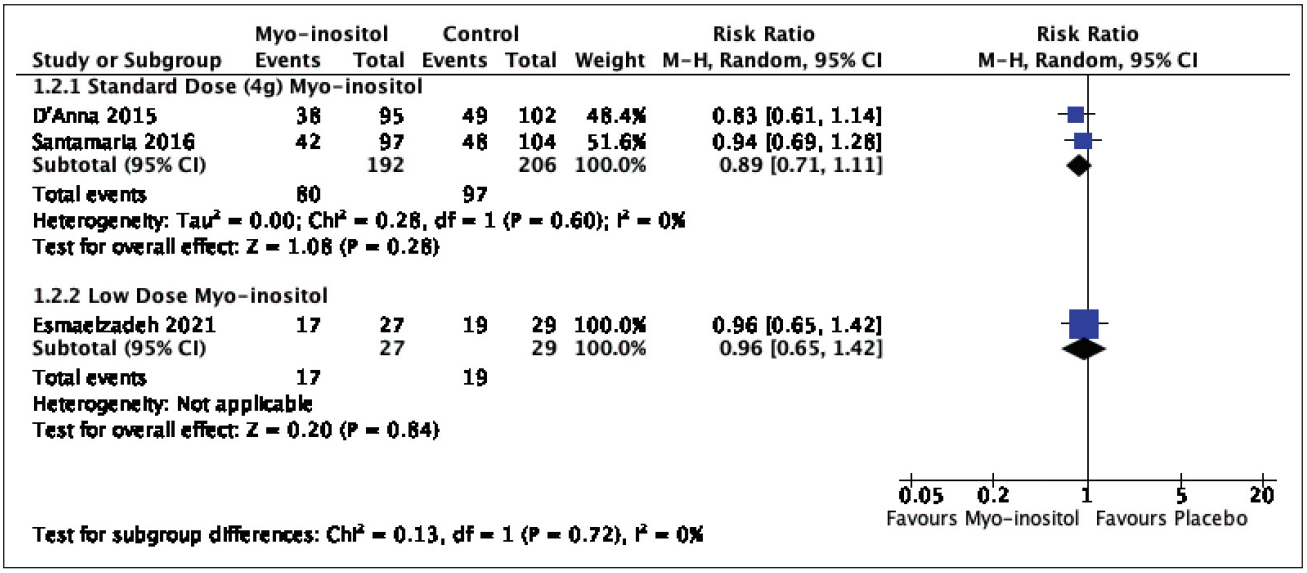

Figure 5. Forest plot of the effect of myo-inositol on the Cesarean Section rate in overweight and obese pregnant women.

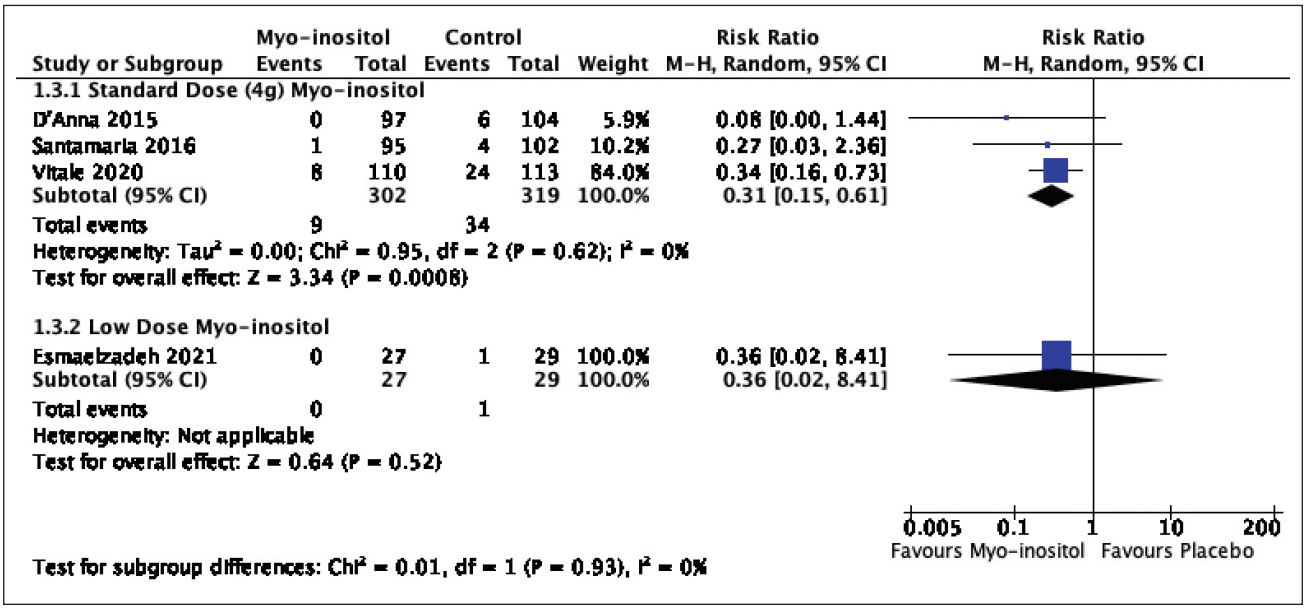

Figure 6. Forest plot of the effect of myo-inositol on the incidence of pregnancy-induced hypertension in overweight and obese pregnant women.

with 95% CI [0.71, 1.11], while for low dose myo-inositol, RR was 0.96 with 95% CI [0.65 to 1.42] as seen in Figure 5.

Based on the evidence, both 4 g myo-inositol and low-dose myo-inositol do not reduce the cesarean section rate in obese and overweight pregnant women. Evidence was of moderate to low certainty because of the serious risk of bias and imprecision.

Incidence of pregnancy-induced hypertension

Four studies as seen in Figure 6 examined the incidence of pregnancy-induced hypertension (PIH).[8,9,11,13] For the studies that used the standard dose of myo-inositol, the relative risk of PIH is 0.31 with 95% CI [0.15, 0.61], (3 trials, n = 621; random effects model). Standard dose myo-inositol seems to reduce the incidence of PIH, but this is based on very low certainty of evidence. The evidence of the benefit of 4 g myo-inositol in decreasing PIH was downgraded to very low because of the serious risk of bias in the studies included and the very serious imprecision in D'Anna and Santamaria, where the confidence intervals crossed the line of no benefit.

For low-dose myo-inositol, while the relative risk is 0.36, the 95% CI [0.02, 8.41] is too wide and crosses the line of no benefit. Low-dose myo-inositol does not decrease the incidence of PIH, based on low certainty of evidence due to very serious imprecision.

Incidence of pre-term birth

Three trials studied the incidence of preterm delivery in overweight and obese women who took myo-inositol.[8,9,13]

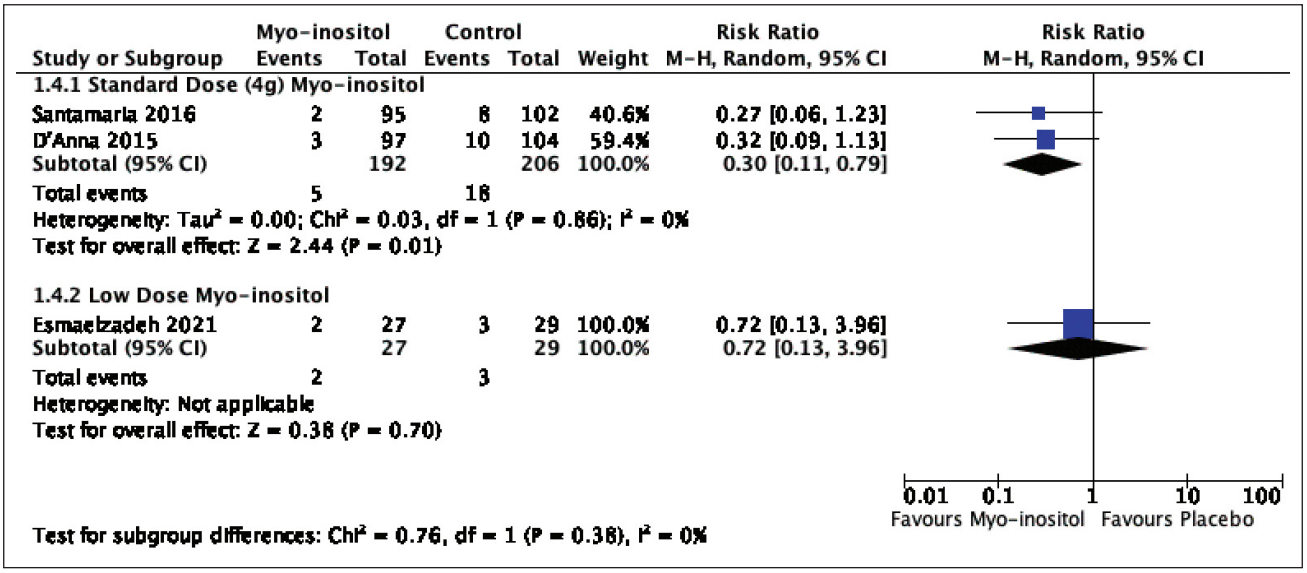

Figure 7. Forest plot of the effect of myo-inositol on the incidence of pre-term birth in overweight and obese pregnant women.

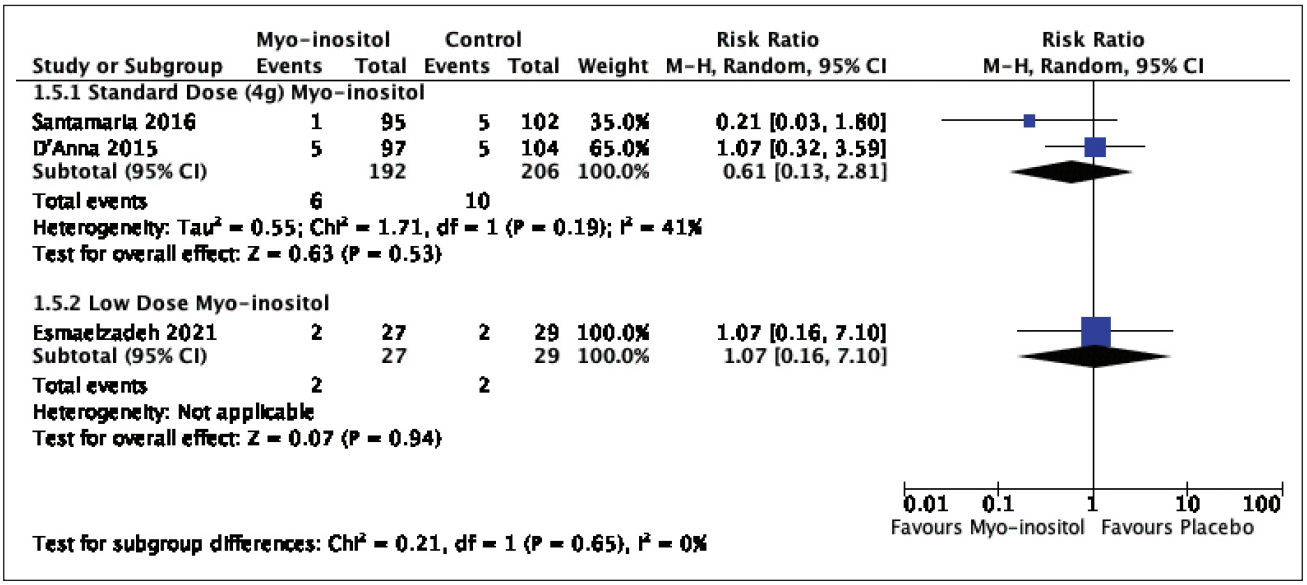

Figure 8. Forest plot of the effect of myo-inositol on the incidence of macrosomia in overweight and obese pregnant women.

In the subgroup of women who received standard dose myo-inositol, the RR was 0.30 with 95% CI [0.11, 0.61], (2 studies; n = 398), while for those given low dose myo-inositol, the RR was 0.72 with 95% CI [0.13, 3.96], (1 study, n = 56).[8,9,13] This is shown in Figure 7.

The evidence suggests that standard dose myo-inositol results in a slight reduction in the incidence of pre-term birth but certainty of evidence is low because of the serious risk of imprecision across the studies included. For low-dose myo-inositol, the evidence suggests that it does not decrease the risk of pre-term birth. The evidence is of low certainty because of the very wide confidence interval that crosses the line of no benefit in Esmaelzadeh.[13]

Incidence of macrosomia

One of the complications of gestational diabetes mellitus is the increased risk for macrosomia. Figure 8 shows the three studies that looked into the incidence of macrosomia in obese and pregnant women.[8,9,13]

In patients given standard dose myo-inositol, the RR was 0.61 with 95% CI [0.13, 2.81], (2 studies; n = 398). Since the confidence interval crossed the line of no benefit, the evidence suggests that myo-inositol does not decrease the incidence of macrosomia compared to standard micro-nutrient supplementation. The certainty of the evidence was downgraded to low because of the serious risk of performance bias, inconsistency across studies and imprecision in the pooled outcome. Low-dose myo-inositol, (RR 1.07 95% CI [0.16, 7.10], 1 study; n = 56), does not decrease the incidence of macrosomia in overweight and obese pregnant women. The certainty of the evidence was low due to the serious risk of bias and very wide confidence interval.[8,9,13]

DISCUSSION

Summary of main results

Evidence from six studies demonstrates a possible benefit of 4 g myo-inositol in reducing the incidence of gestational diabetes mellitus among overweight or obese pregnant women, but the evidence is uncertain. None of the studies reported serious adverse events from myo-inositol (Table 2).

For the secondary outcomes, there is a trend of reduction in the incidence of pre-term birth and incidence of pregnancy-induced hypertension in the standard dose (4 g) myo-inositol group, but the evidence is uncertain. The certainty of the evidence was downgraded because of the high risk of bias from the open-label design of the studies and the wide confidence intervals across the studies and in the pooled effects (Table 2).

Overall completeness and applicability of evidence

Participants in the included trials were pregnant women classified as overweight and obese or those with a BMI of 25 kg/m^2 or greater. These patients were at higher risk of developing GDM compared to women with normal BMI. Although one study included participants with different ethnicities, and another study conducted in the Middle East, the majority of the participants were Caucasians; hence applicability may be limited.

Certainty of evidence

Using GRADEpro, we determined the certainty of the current evidence for the incidence of GDM, caesarian section, pregnancy-induced hypertension, macrosomia and pre-term birth to be very low to low (Table 3).

The review results are based on six randomized controlled trials; three included trials were open-label in design and hence were assigned a high risk of bias in the parameter of blinding of participants and personnel. The certainty of the evidence was also downgraded because some results were inconsistent across studies. Due to the small number of patients and few observed events, the pooled results are less precise and confidence intervals are wide.

Potential biases in the review process

Communication was done through electronic mail with authors of studies when further information or clarification was needed. However, the literature search was limited to English-language articles.

CONCLUSIONS

Implications for practice

Supplementation with myo-inositol to reduce the risk of gestational diabetes mellitus among overweight or obese women is not currently in management guidelines. While evidence from this review demonstrated a possible benefit in the reduction of the incidence of GDM among overweight and obese pregnant women, certainty of the evidence is very low due to the high risk of bias (i.e., open-label design of many of the included studies), inconsistency of study results, and imprecision. The relatively small representation of other ethnicities with a high risk of gestational diabetes mellitus may also limit the applicability of current evidence.

In addition, the safety data evaluated was only for adverse events, and no long-term outcomes such as IQ, BMI or incidence of developmental delay among offspring of women given myo-inositol were reported.

Future high-quality clinical trials may provide more compelling evidence to support practice recommendations. At the moment, there is not enough evidence to support its clinical use for preventing GDM among overweight and obese women.

Implications for research

Applicability may be limited due to predominantly Caucasian participants in the included studies; hence future trials with representative ethnicities are recommended. Trials that reduce the risk of performance bias by ensuring the blinding of participants will also improve evidence quality.

Registration
This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on May 15, 2022 (CRD42022330250). Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022330250

Availability of data collection forms
Data collection forms and extracted data are available upon request to the corresponding author.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
PAF: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **HUC:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration.

Conflict of Interest
The authors have no conflicts of interest to disclose.

Funding Source
None.

Table 2. Summary of findings: Myo-inositol compared to standard micronutrient supplementation for prevention of GDM in overweight and obese pregnant women

Patient or population: prevention of GDM in overweight and obese pregnant women
Intervention: Myo-inositol
Comparison: standard micronutrient supplementation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard micronutrient supplementation	Risk with Myo-inositol				
Incidence of Gestational Diabetes Mellitus						
Standard Dose (4 g) Myo-inositol	284 per 1,000	153 per 1,000 (85 to 273)	RR 0.54 (0.30 to 0.96)	887 (4 RCTs)	⨁◯◯◯ Very low[a,b,c]	Four grams myo-inositol may reduce/have little to no effect on incidence of gestational diabetes mellitus but the evidence is very uncertain.
Low Dose Myo-inositol	287 per 1,000	204 per 1,000 (40 to 1,000)	RR 0.71 (0.14 to 3.50)	176 (2 RCTs)	⨁◯◯◯ Very low[d,e,f]	The evidence is very uncertain about the effect of low dose myo-inositol on incidence of gestational diabetes mellitus.
Cesarean Section Rate						
Standard Dose (4 g) Myo-inositol	471 per 1,000	419 per 1,000 (334 to 523)	RR 0.89 (0.71 to 1.11)	398 (2 RCTs)	⨁⨁◯◯ Low[g,h]	The evidence suggests that 4 g myo-inositol does not reduce cesarean section rate.
Low Dose Myo-inositol	655 per 1,000	629 per 1,000 (426 to 930)	RR 0.96 (0.65 to 1.42)	56 (1 RCT)	⨁⨁⨁◯ Moderate[i]	Two grams myo-inositol probably does not reduce cesarean section rate
Incidence of Pregnancy Induced Hypertension						
Standard Dose (4 g) Myo-inositol	107 per 1,000	33 per 1,000 (16 to 65)	RR 0.31 (0.15 to 0.61)	621 (3 RCTs)	⨁◯◯◯ Very low[a,j]	Four grams myo-inositol may reduce/have little to no effect on pregnancy induced hypertension but the evidence is very uncertain.
Low Dose Myo-inositol	34 per 1,000	12 per 1,000 (1 to 290)	RR 0.36 (0.02 to 8.41)	56 (1 RCT)	⨁⨁◯◯ Low[k]	The evidence suggests that 2 g myo-inositol does not reduce pregnancy induced hypertension.
Incidence of Pre-term Birth						
Standard Dose (4 g) Myo-inositol	87 per 1,000	26 per 1,000 (10 to 69)	RR 0.30 (0.11 to 0.79)	398 (2 RCTs)	⨁⨁◯◯ Low[a,l]	The evidence suggests 4 g myo-inositol results in a slight reduction in incidence of pre-term birth.
Low Dose Myo-inositol	103 per 1,000	74 per 1,000 (13 to 410)	RR 0.72 (0.13 to 3.96)	56 (1 RCT)	⨁⨁◯◯ Low[m]	The evidence suggests that 2 g myo-inositol does not reduce incidence of pre-term birth.
Incidence of Macrosomia						
Standard Dose (4 g) Myo-inositol	49 per 1,000	30 per 1,000 (6 to 136)	RR 0.61 (0.13 to 2.81)	398 (2 RCTs)	⨁◯◯◯ Very low[a,i,n,o]	The evidence is very uncertain about the effect of 4 g myo-inositol on incidence of macrosomia.
Low Dose Myo-inositol	69 per 1,000	74 per 1,000 (11 to 490)	RR 1.07 (0.16 to 7.10)	56 (1 RCT)	⨁⨁◯◯ Low[p]	Two grams myo-inositol may result in little to no difference in incidence of macrosomia.

*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 certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations:
a. Very serious risk of bias because D'Anna 2015, Santamaria 2016, and Vitale 2020 were open-label studies.
b. Serious inconsistency, in Godfrey 2021, the intake of myo-inositol is of no clear benefit from placebo in GDM incidence with a RR 1.05 (95% CI = 0.73, 1.51) compared to the other 3 studies (D'Anna 2015, Santamaria 2016, and Vitale 2020) which all showed benefit.
c. Serious imprecision, the RR for developing GDM in the 4 g dose group is 0.54 but the 95% CI = 0.30, 0.96 is very wide.
d. Serious risk of bias, for Farren 2017, there was no mention of blinding of participants, personnel, and outcome assessors.
e. Serious inconsistency - Farren 2017 showed an increase in the incidence of GDM, while Esmaelzadeh 2022 showed some benefit.
f. Serious imprecision - the confidence interval for preventing GDM is very wide, RR 0.71 95% CI = 0.14, 3.50.
g. Very serious risk of bias because D'Ana 2015 and Santamaria 2016 are both open-label studies.
h. Serious imprecision - the confidence intervals of the individual studies and the pooled effects are wide and cross the line of no benefit.
i. Serious imprecision - the confidence interval is wide for Esmaelzadeh 2022.
j. Very serious imprecision - D'Anna 2015 and Santamaria 2016 have wide confidence intervals that crossed the no-effect line.
k. Serious imprecision - The Esmaelzadeh 2022 study has a very wide confidence interval for PIH (95% CI = 0.02, 8.41) which crosses the line of no effect.
l. Serious imprecision - The confidence interval for both D'Anna 2015 and Santamaria 2016 crossed the line of no benefit.
m. Very serious imprecision - The confidence interval for the Esmaelzadeh 2022 study in reducing the risk of pre-term birth is very wide, with 95% CI = 0.16, 7.1.
n. Serious inconsistency - Santamaria 2016 showed a trend toward benefit in terms of macrosomia, while D'Anna 2015 showed no benefit of giving myo-inositol for decreasing macrosomia. Furthermore, the pooled effects crossed the line of no benefit.
o. Very serious imprecision - there was a wide confidence interval on the effect of 4 g myo-inositol on the incidence of fetal macrosomia.
p. Very serious imprecision - For the Esmaelzadeh 2021 study, the confidence interval for the incidence of macrosomia was wide, with 95% CI = 0.16, 7.1.

Table 3. Myo-inositol compared to standard micronutrient supplementation for prevention of GDM in overweight and obese pregnant women

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard micronutrient supplementation	With Myo-inositol	Relative effect (95% CI)	Risk with standard micronutrient supplementation	Risk difference with Myo-inositol
Incidence of Gestational Diabetes Mellitus - Standard Dose (4 g) Myo-inositol											
887 (4 RCTs)	very serious[a]	serious[b]	not serious	serious[c]	none	⨁◯◯◯ Very low	127/447 (28.4%)	77/440 (17.5%)	RR 0.54 (0.30 to 0.96)	284 per 1,000	131 fewer per 1,000 (from 199 fewer to 11 fewer)
Incidence of Gestational Diabetes Mellitus - Low Dose Myo-inositol											
176 (2 RCTs)	serious[d]	serious[e]	not serious	serious[f]	none	⨁◯◯◯ Very low	25/87 (28.7%)	25/89 (28.1%)	RR 0.71 (0.14 to 3.50)	287 per 1,000	83 fewer per 1,000 (from 247 fewer to 718 more)
Cesarean Section Rate - 4 g Myo-inositol											
398 (2 RCTs)	serious[g]	not serious	not serious	serious[h]	none	⨁⨁◯◯ Low	97/206 (47.1%)	80/192 (41.7%)	RR 0.89 (0.71 to 1.11)	471 per 1,000	52 fewer per 1,000 (from 137 fewer to 52 more)
Cesarean Section Rate - 2 g Myo-inositol											
56 (1 RCT)	not serious	not serious	not serious	serious[i]	none	⨁⨁⨁◯ Moderate	19/29 (65.5%)	17/27 (63.0%)	RR 0.96 (0.65 to 1.42)	655 per 1,000	26 fewer per 1,000 (from 229 fewer to 275 more)
Pregnancy Induced Hypertension - 4 g Myo-inositol											
621 (3 RCTs)	very serious[a]	not serious	not serious	very serious[j]	none	⨁◯◯◯ Very low	34/319 (10.7%)	9/302 (3.0%)	RR 0.31 (0.15 to 0.61)	107 per 1,000	74 fewer per 1,000 (from 91 fewer to 42 fewer)
Pregnancy Induced Hypertension - 2 g Myo-inositol											
56 (1 RCT)	not serious	not serious	not serious	very serious[k]	none	⨁⨁◯◯ Low	1/29 (3.4%)	0/27 (0.0%)	RR 0.36 (0.02 to 8.41)	34 per 1,000	22 fewer per 1,000 (from 34 fewer to 256 more)
Incidence of Pre-term Birth - 4 g Myo-inositol											
398 (2 RCTs)	serious[a]	not serious	not serious	serious[l]	none	⨁⨁◯◯ Low	18/206 (8.7%)	5/192 (2.6%)	RR 0.30 (0.11 to 0.79)	87 per 1,000	61 fewer per 1,000 (from 78 fewer to 18 fewer)
Incidence of Pre-term Birth - 2 g Myo-inositol											
56 (1 RCT)	not serious	not serious	not serious	very serious[m]	none	⨁⨁◯◯ Low	3/29 (10.3%)	2/27 (7.4%)	RR 0.72 (0.13 to 3.96)	103 per 1,000	29 fewer per 1,000 (from 90 fewer to 306 more)
Incidence of Macrosomia - 4 g Myo-inositol											
398 (2 RCTs)	serious[a]	very serious[n]	not serious	very serious[i,o]	none	⨁◯◯◯ Very low	10/206 (4.9%)	6/192 (3.1%)	RR 0.61 (0.13 to 2.81)	49 per 1,000	19 fewer per 1,000 (from 42 fewer to 88 more)
Incidence of Macrosomia - 2 g Myo-inositol											
56 (1 RCT)	not serious	not serious	not serious	very serious[p]	none	⨁⨁◯◯ Low	2/29 (6.9%)	2/27 (7.4%)	RR 1.07 (0.16 to 7.10)	69 per 1,000	5 more per 1,000 (from 58 fewer to 421 more)

CI: confidence interval; RR: risk ratio

Explanations
a. Very serious risk of bias because D'Anna 2015, Santamaria 2016, and Vitale 2020 were open-label studies.
b. Serious inconsistency, in Godfrey 2021, the intake of myo-inositol is of no clear benefit from placebo in GDM incidence with a RR 1.05 (95% CI = 0.73, 1.51) compared to the other 3 studies (D'Anna 2015, Santamaria 2016, and Vitale 2020) which all showed benefit.
c. Serious imprecision, the RR for developing GDM in the 4 g dose group is 0.54 but the 95% CI = 0.30, 0.96 is very wide.
d. Serious risk of bias, for Farren 2017, there was no mention of blinding of participants, personnel, and outcome assessors.
e. Serious inconsistency - Farren 2017 showed an increase in the incidence of GDM, while Esmaelzadeh 2022 showed some benefit.
f. Serious imprecision - the confidence interval for preventing GDM is very wide, RR 0.71 95% CI = 0.14, 3.50.
g. Very serious risk of bias because D'Ana 2015 and Santamaria 2016 are both open-label studies.
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n. Serious inconsistency - Santamaria 2016 showed a trend toward benefit in terms of macrosomia, while D'Anna 2015 showed no benefit of giving myo-inositol for decreasing macrosomia. Furthermore, the pooled effects crossed the line of no benefit.
o. Very serious imprecision - there was a wide confidence interval on the effect of 4 g myo-inositol on the incidence of fetal macrosomia.
p. Very serious imprecision - For the Esmaelzadeh 2021 study, the confidence interval for the incidence of macrosomia was wide 95% CI = 0.16, 7.1

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