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REVIEW

Inositol for the prevention of gestational diabetes: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Purpose Inositol (ISL) embraces a family of simple carbohydrates with insulin-sensitizing properties, whose most common isoforms are Myo-inositol (MYO) and D-chiro inositol (DCI). The aim of the present study was to assess the efficacy and safety of ISL supplementation during pregnancy for the prevention of gestational diabetes (GDM).

Methods We conducted a systematic literature search in electronic databases until October 2017. We included all randomized controlled trials (RCTs) comparing pregnant women with GDM who were randomized to either ISL (i.e., intervention group) or either placebo or no treatment (i.e., control group). The primary outcome was the preventive effect on GDM, defined as the rate of GDM in women without a prior diagnosis of GDM. Pooled results were expressed as odds ratio (OR) with a 95% confidence interval (95% CI).

Results Five RCTs were included (including 965 participants). ISL supplementation was associated with lower rate of GDM (OR 0.49, 95% CI 0.24–1.03, $p=0.01$) and lower preterm delivery rate (OR 0.35, 95% CI 0.17–0.74, $p=0.006$). No adverse effects were reported. Adjusting for the type of intervention (MYO 2 g twice daily vs MYO 1100 mg plus DCI 27.6 mg daily), a significant effect was found only in patients receiving 2 g MYO twice daily.

Conclusions ISLs administration during pregnancy appears to be safe and may represent a novel strategy for GDM prevention. In particular, the double administration of MYO 2 g per day may improve the glycemic homeostasis and may reduce GDM rate and preterm delivery rate.

Keywords Inositol · Gestational diabetes · Diabetes prevention · Preterm delivery · Maternal–fetal health

Introduction

Gestational diabetes mellitus (GDM) is defined as a status of glucose intolerance in pregnant women without a previous diagnosis of diabetes [1]. It affects about 7% of pregnant women worldwide and is associated with higher risk of pregnancy complications, such as gestational hypertension, macrosomia, shoulder dystocia, preterm delivery, cesarean delivery, neonatal hypoglycemia and increased perinatal mortality [2, 3].

Inositol (ISL) is a sixfold alcohol of cyclohexane that is present in animal and plant cells [4, 5]. ISLs family comprises nine stereoisomers who are constituent parts of cellular membrane, regulating mitochondria function and different hormonal signaling in the human body [6, 7]. Myo inositol (MYO) and D-chiro inositol (DCI), the most common isoforms of ISL in eukaryotic cells, are characterized by

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insulin-mimetic properties with potential therapeutic effects on insulin-mediated disease [8, 9].

In last years, different studies have investigated the preventive effects of inositol (ISL) supplementation for GDM [8, 10]. Nevertheless, a recent Cochrane review concluded that the body of evidence on ISLs effectiveness for this purpose was poor [11]. In last year, two additional randomized controlled trials (RCTs) [12, 13] have investigated this topic. Thus, the aim of this systematic review and meta-analysis was to assess the efficacy and safety of the administration of ISLs during pregnancy for the prevention of GDM.

Materials and methods

Study design

This study was conducted according to a protocol designed a priori and recommended for systematic review. Review was reported following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [14].

Search strategy

We conducted a systematic literature search in electronic databases (Pubmed, Embase, Science direct, the Cochrane library, Clinicaltrials.gov, Cochrane Central Register of Controlled Trials, EU Clinical Trials Register and World Health Organization International Clinical Trials Registry Platform) until October 2017, without date restriction. The Key search terms included: inositol OR myo inositol OR D-chiro inositol (Mesh/Emtree) AND pregnancy OR gestational diabetes.

No built-in search filters were applied to limit citations retrieval. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches.

Inclusion criteria

We included all randomized controlled trials evaluating the effects of ISLs (MYO and/or DCI) administration during pregnancy in women at risk of GDM, in whom the control group received no intervention or placebo. Studies were included if exploring the primary and/or the secondary outcomes of the review.

Review outcomes

The Primary Outcome was to compare the rate of GDM in patients receiving ISLs with patients not receiving intervention (Controls). The Secondary Outcomes were to determine the effects of preventive ISL administration on maternal and feto-neonatal health, as well as on delivery outcomes. Moreover, we evaluated the side effects associated with the intervention.

Outcomes measures

- Maternal health outcomes measures:
  - *GDM rate* Defined as the number of patients (%) in which GDM was diagnosed.
  - *Fasting Glucose OGTT (FG-OGTT), 1 h Glucose OGTT (1HG-OGTT), 2 h Glucose OGTT (2HG-OGTT)* Defined, respectively, as the mean (mg/dl) fasting plasma glucose level, 1-h plasma glucose level and 2-h plasma glucose level at OGTT.
  - *Weight gain at OGTT* Defined as the mean weight increase (kg) from the start of ISLs assumption to OGTT.
  - *Hypertensive disorders (%)* Defined as the occurrence of pregnancy-induced hypertension or preeclampsia.
  - *Total cholesterol, LDL, HDL, triglycerides after 30/60 days* Defined as the mean (mg/dl) serum cholesterol, LDL (mg/dl), HDL (mg/dl) and triglycerides (mg/dl) at day 30 and 60 of INSs administration.
  - *Systolic blood pressure (SBP) and diastolic blood pressure (DBP) after 30/60 days* Defined as the mean (mmHg) systolic and diastolic blood pressure levels at days 30 and 60 of INSs administration.
- Delivery outcomes measures:
  - *Cesarean section rate (CS Rate)* Defined as the number of patients (%) in which Cesarean Section was performed.
  - *Preterm delivery (%)* Defined as the birth of a baby at fewer than 37 weeks gestational age.
  - *Shoulder dystocia (%)* Defined as the occurrence of shoulder dystocia during labor.
  - *Third degree perineal tear (%)* Defined as the laceration of external anal sphincter.
- Feto-neonatal health outcomes measures:
  - *Gestational age at birth (GA at birth)* Defined as the days of gestation (mean) at the time of delivery.
  - *Birth weight* Defined as the mean neonatal weight (kg) at birth.
  - *Macrosomia (%)* Defined as a birth weight $\geq$4000 g.
  - *Neonatal hypoglycemia (%)* Defined as a plasma glucose level of less than 30 mg/dl.
  - *Neonatal Intensive Care Unit admission (NICU admission)*: Defined as the onset of neonatal complications (%) necessitating for intensive care.

- *Polyhydramnios (%)* Defined as amniotic fluid index above the 95th percentile.
- *Fetal biometry measures* Defined as the (mean) percentiles of fetal biparietal diameter (BPD), head circumference (HC), femur length (FL) and abdominal circumference (AC).

- Side effects:
  Any untoward medical occurrence that may present during treatment (%).

Study selection and data extraction

Two authors (A.V., G.S.), independently, screened titles and abstracts. The full text of all relevant trial reports identified through the searching activities was independently examined. The same authors independently assessed the studies for inclusion and extracted data about study features (country and time of realization of the study), included populations (participants number and main inclusion criteria), type of intervention (drugs and dosage) and study outcomes. If more than one study published by the same group was identified, the corresponding authors were contacted by e-mail in order to avoid duplications. One other author (V.B.) independently reviewed the selection and data extraction process. The results were compared and any disagreement was resolved by consensus.

Risk of bias

The risk of bias within studies was assessed independently by two authors (A.V., G.S.) following the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Seven domains related to risk of bias were assessed in each included trial: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. Review authors' judgments were categorized as "low risk", "high risk" or "unclear risk" of bias.

Data analysis

Data analysis was performed by two authors (A.V., G.S.) using Review Manager Version 5.3 (The Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). Results were compared and differences were discussed.

Continuous variables were compared using the means (and standard deviations) and expressed as mean differences (MD) among Groups (95% CI). Dichotomous variables were compared using the odds ratio (OR) with a 95% confidence interval (95% CI). Significance level was set at $p < 0.05$. Heterogeneity was measured using *I*-squared (Higgins I^2). All analyses were carried out using the random effects model (of DerSimonian and Laird, assuming that the patients analyzed were drawn from a hierarchy of different populations). Subgroup analyses were performed to evaluate the specific influence of different inositol subtypes (MYO, MYO plus DCI, DCI) on pooled ORs and MDs.

We aimed to assess Publication Bias with the use of Funnel plot if at least ten studies were included in the meta-analysis, according to Cochrane Handbook Recommendations.

Grading of evidence

The evidence was rated by one author (A.V.) using grading of recommendations assessment development and evaluation working group (GRADE) methodology (GRADE Pro software, available at https://gradepro.org/). The GRADE criteria allow the assessment of a body of evidence in terms of study design, risk of bias, indirectness, inconsistency, imprecision, large effect size, plausible confounding, dose response gradient and publication bias.

The body of evidence was qualified for the following outcomes: GDM rate, hypertensive disorders, preterm delivery, macrosomia, CS rate, neonatal hypoglycemia, and NICU admission.

Results

Study selection

After the evaluation of full text, eight studies were excluded [6, 15–21]. Finally, a total number of five studies [12, 13, 22–24] were included in the present meta-analysis (see Figure S1).

Included studies

The five trials included embedded a total number of 965 participants. A summary of main characteristics of the included studies is available in Table 1.

Study setting and blinding

Four studies were conducted in Italy [12, 22–24] and one study in Ireland [13]. Three were double-center studies [12, 22, 24] and the remaining two trials were carried out in a single center [13, 23]. One study was double-blinded [22]. Remaining studies were open label for both clinicians and outcomes assessors [12, 13, 23, 24].

Table 1 General features of the studies

References	Country and time of realization	Participants and main inclusion criteria	Intervention and timing	Intervention group	Control group	Maternal health outcomes	Delivery outcomes	Feto-neonatal health outcomes
D' Anna et al. [23]	Italy From beginning 2010 (duration: 2 years)	220 pregnant women (23 patients excluded) Caucasian ethnicity I degree familiarity for T2D BMI < 30 kg/m^2 FPG < 126 mg/dl RG < 200 mg/dl Singleton pregnancy no corticosteroid treatment no PCOS	2 g MYO twice a day plus 200 µg folic acid From 12 to 13 GW	Group A (n = 99) Age: 31.0 ± 5.3 BMI: 22.8 ± 3.1	Group B (n = 98) 200 µg folic acid daily Age: 31.6 ± 5.6 BMI: 23.6 ± 3.1	GD onset FG-OGTT 1 h-OGTT 2 h-OGTT GH Weight increase Adverse events	CS rate Preterm delivery Shoulder dystocia	Macrosomia Birth weight GA at birth Neonatal hypoglycemia
Malvasi et al. [22]	Italy January–December 2012	65 pregnant women (17 patients excluded 26.1%) Healthy Age 30–40 years BMI 25–30 kg/m^2	2 g MYO, 400 mg DCI, 400 µg folic acid, 10 mg manganese. From 13 to24 GW	Group A (n = 24) Age: 32.2 ± 5.46 BMI: 26.98 ± 0.22	Group B (n = 24) Placebo Age: 31.58 ± 5.66 BMI: 26.8 ± 0.22	30–60 day LDL 30–60 day HDL 30–60 day TC 30–60 day SBP 30–60 day DBP Adverse events	–	–
D' Anna et al. [23] *[NCT01047982]*	Italy January 2011–April 2014	220 pregnant women (19 patients did not complete the study) BMI ≥ 30 kg/m^2 FPG < 126 mg/dl RG < 200 mg/dl Singleton pregnancy First-trimester glycosuria ≥ 10 mg/dL No corticosteroid treatment No renal, hepatic, hypertensive disorders	2 g MYO plus 200 µg folic acid twice a day From 12 to 13 GW	Group A (n = 97) Age: 30.09 (18–44) BMI: 33.8 (30–46.9)	Group B (n = 104) 200 µg folic acid twice a day Age: 31.7 (19–43) BMI: 33.8 (30–46)	GD onset FG-OGTT 1 h-OGTT 2 h-OGTT GH Weight increase Adverse events	CS rate Preterm delivery Shoulder dystocia	Macrosomia Birth weight GA at birth Neonatal hypoglycemia NICU admission

Table 1 (continued)

References	Country and time of realization	Participants and main inclusion criteria	Intervention and timing	Intervention group	Control group	Maternal health outcomes	Delivery outcomes	Feto-neonatal health outcomes
Santamaria et al. [12] *[NCT01047982]*	Italy From beginning 2012 (duration: 36 months)	220 pregnant women (23 patients did not complete the study) Caucasian ethnicity BMI > 25 and < 30 kg/m^2 FPG < 126 mg/dl RG < 200 mg/dl Singleton pregnancy no first-trimester glycosuria no corticosteroid treatment no previous GDM	2 g MYO twice a day plus 200 µg folic acid From 12 to 13 GW	Group A ($n = 95$) Age: 32.1 ± 4.8 BMI: 26.9 ± 1.3	Group B ($n = 102$) 200 µg folic acid twice a day Age: 32.7 ± 5.3 BMI: 27.1 ± 1.3	GD onset FG-OGTT 1 h-OGTT 2 h-OGTT GH Weight increase Adverse events	CS rate Preterm delivery Shoulder dystocia	Macrosomia Birth weight GA at birth Neonatal hypoglycemia NICU admission
Farren et al. [13] *[ISRCTN92466608]*	Ireland January 2014–January 2016	240 pregnant women (6 patients did not complete the study) I degree familiarity for T2D Singleton pregnancy Age ≥ 18 years Pre-existing liver/kidney disease or diabetes.	MYO 1100 mg, DCI 27.6 g, and 400 µg folic acid per day From 10 to 16 GW	Group A ($n = 120$) Age: 31.1 ± 5.1 BMI: 26 ± 5.3	Group B ($n = 120$) 400 µg folic acid per day Age: 31.5 ± 5 BMI: 26.2 ± 5.5	GD onset FG-OGTT 1 h-OGTT 2 h-OGTT GH Adverse events	CS rate Induced labor Preterm delivery Shoulder dystocia Perineal trauma (third degree)	Macrosomia Birth weight GA at birth Neonatal hypoglycemia NICU admission

Study drugs

Three studies [12, 23, 24] compared the administration of 2 g MYO twice/day with placebo; one study [13] evaluated the effects of MYO 1100 mg plus DCI (27.6 mg) versus placebo; another study [22] investigated the effects of 2 g MYO plus 400 mg DCI plus 10 mg manganese versus placebo.

Placebo was folic acid (200 µg capsules) in four studies [12, 13, 23, 24], while in the study by Malvasi et al. [22] placebo content was not clarified.

Type of patients

Four studies included exclusively singleton pregnancies [12, 13, 23, 24], while in the study by Malvasi et al. [22] the number of fetuses was not specified.

Patients' BMI was between 25 and 30 (kg/m^2) in two studies [12, 22], ≥ 30 in one study [24] and < 30 in the study by D'Anna et al. [23]. In Farren et al. study [13], patients' BMI was variable.

Finally, two studies [13, 23] included only patients with familiarity (of first degree) for Type II diabetes.

Diagnosis of gestational diabetes

In four studies [12, 13, 23, 24], diagnosis of GDM was based on International Association of Diabetes and Pregnancy Study Groups Consensus Panel 2010 criteria [25]. In Malvasi et al.'s study [22], the diagnostic criteria for GDM were not specified (GDM rate was not a study outcome).

Assessment of the risk of study BIAS

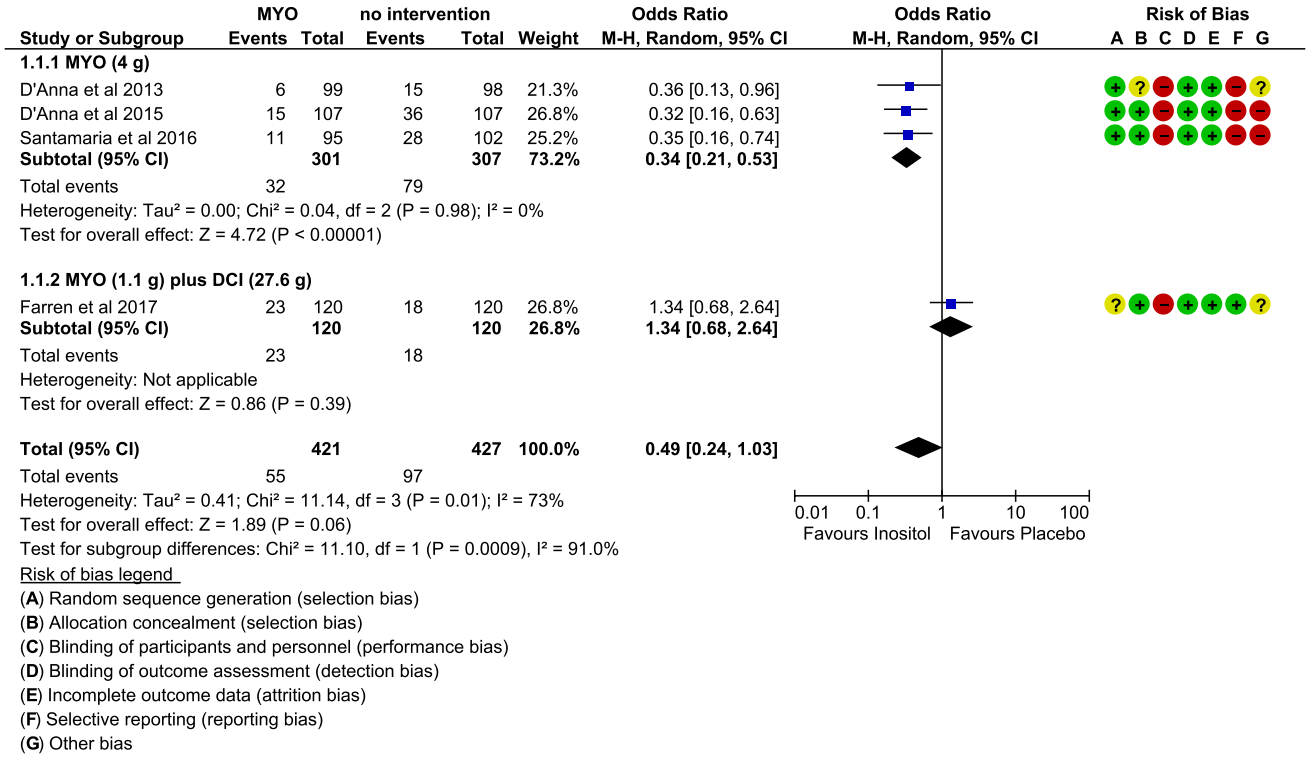
- *Selection bias* All but one study [13] (who did not provide clear information) used an adequate method of random sequence generation (computer generated sequence). In one study [23], the method of allocation was not reported (unclear risk of bias), whilst remaining studies used an adequate allocation strategy (central allocation [24] or sealed envelopes [12, 13, 22]).
- *Performance bias* All but one study [22] were not blinded for both personnel and participants; accordingly, four studies were judged at high risk of bias [12, 13, 23, 24].
- *Detection bias* The outcomes evaluated were unlikely to be influenced by the open-label design of the majority of studies. Therefore, all studies were judged at low risk of bias.
- *Attrition bias* A drop-out of a small number of participants occurred in all studies. However, it was judged as insubstantial in all but one study [22] (26.1% of drop-out), according to Cochrane Handbook Recommendations ("a drop-out not exceeding 20% should not lead to substantial bias").
- *Reporting bias* Two studies were judged at high risk of bias for selective data reporting because the outcomes were redesigned after protocol registration [12, 24]. Two additional studies were considered at high risk of bias because a protocol registration was not reported in the manuscript or found in registers [22, 23].
- *Other bias* All studies were judged at unclear/high risk of other bias: In Farren et al.'s study [13], a disparity between the pre-defined intervention (in the study protocol) and the final intervention was observed in terms of drug posology (unclear risk of bias). Differently, in D' Anna et al.'s study [23] the percentage of patients with a history of GDM (in previous pregnancies) was not reported (unclear risk of bias) due to a non-comprehensive description of methods (i.e., timing/number of blood pressure measurements) [22]. Finally, two studies [12, 24] were flawed by a baseline difference in familiarity for type II diabetes across groups, potentially affecting the effects estimates (Figure S2).

Effects of intervention

ISLs vs no intervention

- Maternal health
  - *GDM rate* Analysis involved a total number of 848 patients ($n = 421$ receiving ISLs and $n = 427$ controls) from four studies [12, 13, 23, 24]. The overall results significantly favoured ISLs (OR 0.49, 95% CI 0.24–1.03, $p = 0.01$), with high degree of heterogeneity across studies ($I^2 = 73\%$) (Fig. 1a)
  - *FG-OGTT, 1HG-OGTT and 2HG-OGTT* Four studies [12, 13, 23, 24] with 854 participants were included ($n = 424$ receiving ISLs and $n = 430$ controls). A significant advantage was observed in ISLs group concerning FG-OGTT (MD = −2.62, [95% CI −4.15, −1.09], $p = 0.0008$, $I^2 = 38\%$), while no difference was observed in 1HG-OGTT (MD = −6.57, [95% CI −14.24, 1.10], $p = 0.09$, $I^2 = 65\%$) and 2HG-OGTT (MD = −5.86, [95% CI −15.20, 3.48], $p = 0.22$, $I^2 = 85\%$) (Fig. 1b–d)
  - *Weight gain at OGTT* Including 608 patients from three studies [12, 23, 24], no difference among groups was observed (MD = −0.04, [95% CI −1.31, 1.38], $p = 0.96$, $I^2 = 82\%$).
  - *Hypertensive disorders* A total number of 829 patients ($n = 408$ receiving ISLs and $n = 421$ controls) were analyzed from four studies [12, 13, 23, 24]. A lower pooled prevalence of hypertensive disorders was found in ISLs group, which was not statistically significant (OR 0.38, 95% CI 0.12–1.16, $p = 0.09$). Inconsistency was low ($I^2 = 20\%$) (Fig. 1e)

(a)



(b)

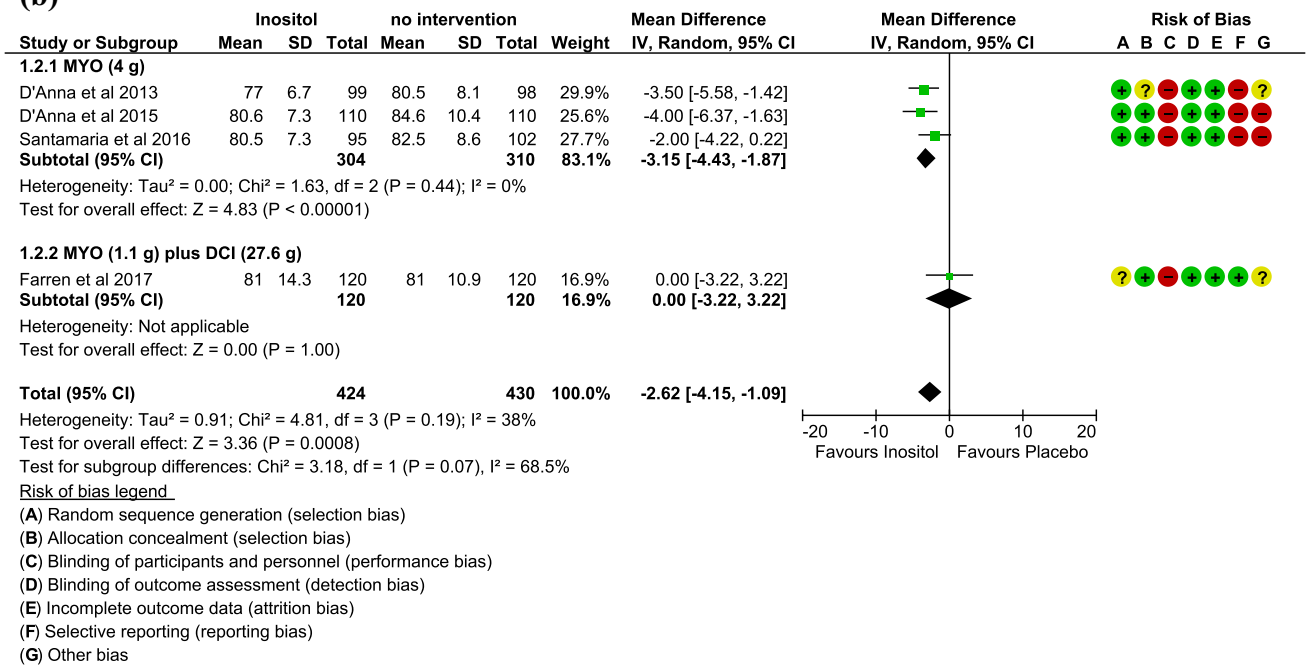
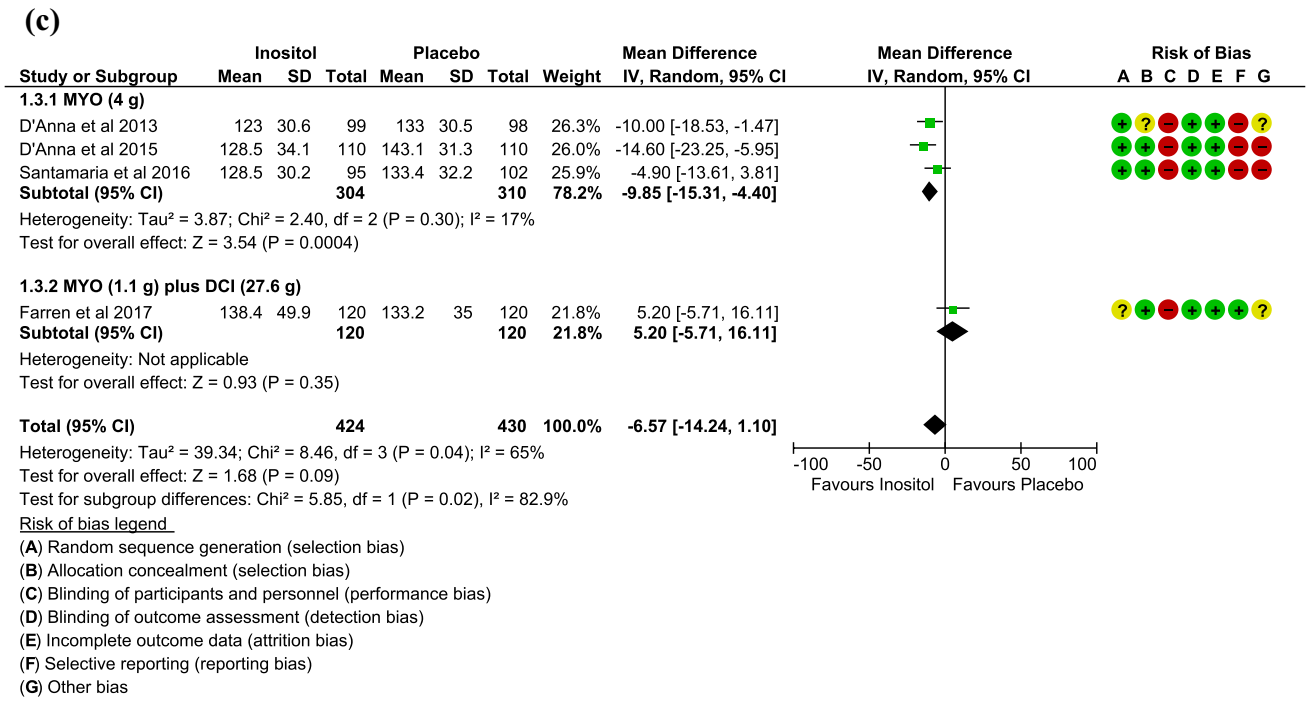


Fig. 1 Inositol vs placebo for GDM prevention: GDM rate (**a**), FG-OGTT (**b**), 1H-OGTT (**c**), 2H-OGTT (**d**), hypertensive disorders (**e**), preterm delivery (**f**)



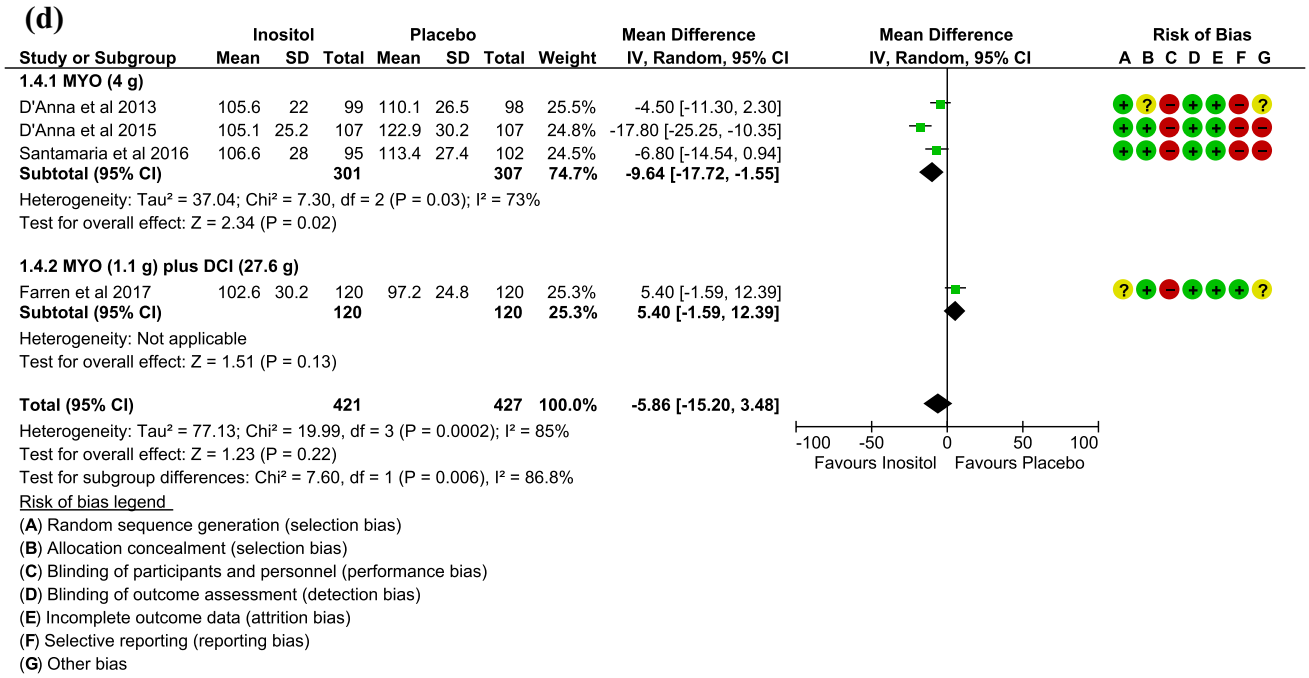
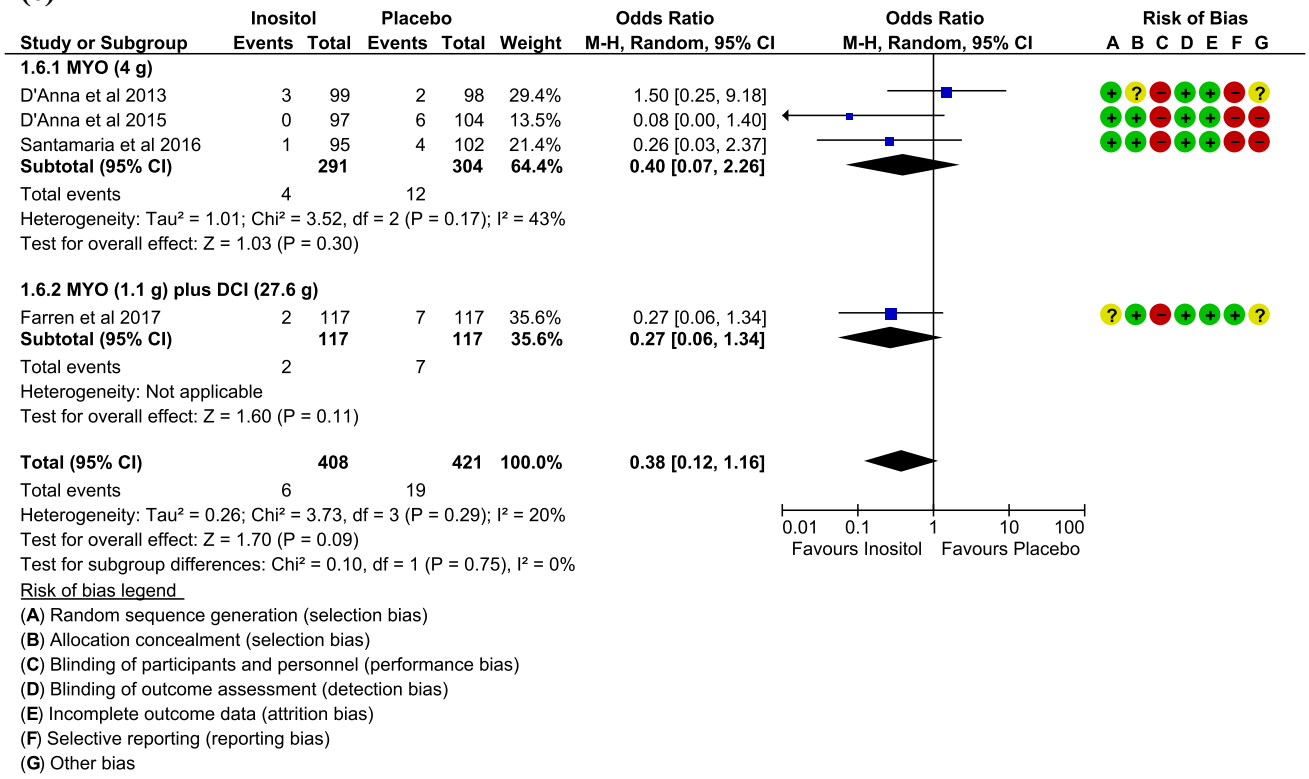


Fig. 1 (continued)

– *Total cholesterol, LDL, HDL, triglycerides after 30/60 days* Only one study [22] including 48 patients ($n=24$ receiving ISLs and $n=24$ controls) reported data about these metabolic markers. At 30 days, a significant lower concentration was observed in total cholesterol (209.54 ± 6.6 vs 225.79 ± 10.67, $p=0.0001$), LDL (141.95 ± 12.57 vs 154.16 ± 12.04, $p=0.001$) and triglycerides (154.91 ± 7.44 vs 170.20 ± 10.32, $p=0.0001$), but not in HDL ($p=0.09$). At 60 days, a significant lower concentration was observed in Total cholesterol (185.37 ± 10.8 vs 232.66 ± 8.82, $p=0.0001$), LDL (124.83 ± 9.90 vs 158.33 ± 11.96, $p=0.0001$), triglycerides (136.37 ± 7.63vs 175.70 ± 8.85,

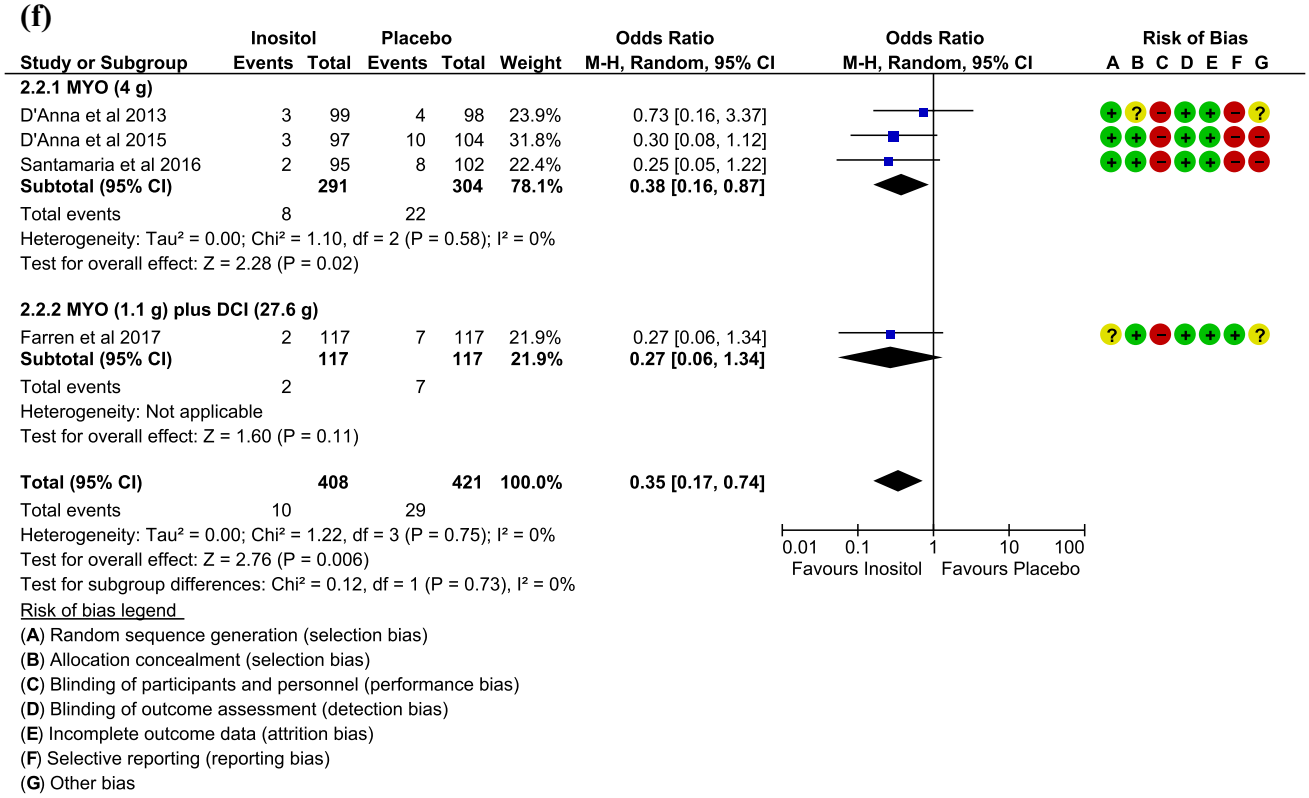
(e)



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

(f)



Risk of bias legend

(**A**) Random sequence generation (selection bias)
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(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Fig. 1 (continued)

$p = 0.0001$), as well as in HDL (60.54 ± 10.25vs 74.33 ± 7.68, $p = 0.0001$).
  - *SBP and DBP after 30/60 days* Data from one study [22] showed a significant difference in SBP after 30 days (119.16 ± 6.53 vs 121.04 ± 6.91, $p = 0.03$), but not after 60 days ($p = 0.12$). No difference was observed in DBP both at 30 ($p = 0.09$) and 60 days ($p = 0.421$).

- Delivery outcomes
  - *CS rate* The analysis of 829 patients ($n = 408$ in ISLs group and $n = 421$ controls) from four studies [12, 13, 23, 24] did not show any difference in CS rate (OR 0.86, 95% CI 0.65–1.13, $p = 0.28$, $I^2 = 0\%$) [24]
  - *Preterm delivery* Data from four studies [12, 13, 23, 24] about 829 patients ($n = 408$ in ISLs group and $n = 421$ controls) showed lower prevalence of Preterm delivery in ISLs group (OR 0.35, 95% CI 0.17–0.74, $p = 0.006$, $I^2 = 0\%$) (Fig. 1f)
  - *Shoulder dystocia* The analysis of 829 patients from four studies [12, 13, 23, 24] did not show any difference in shoulder dystocia occurrence (OR 0.57, 95% CI 0.12–2.71, $p = 0.48$, $I^2 = 0\%$).
  - *Third degree perineal tear* Only one study reported data about perineal lacerations, showing no difference among ISLs group and Controls (OR 3.05, 95% CI 0.31–29.78, $p = 0.34$).

- Feto-neonatal health
  - *GA at birth* Data from four studies [12, 13, 23, 24] about 829 patients ($n = 408$ in ISLs group and $n = 421$ controls) showed no significant difference in GA at birth among groups (MD = 1.34, [95% CI − 0.18, 2.85], $p = 0.08$, $I^2 = 4\%$).
  - *Birth weight and Macrosomia* The analysis of 829 patients from four studies [12, 13, 23, 24] did not show significant difference in birth weight (MD = − 8.65, [95% CI − 140.36, 123.07], $p = 0.90$, $I^2 = 72\%$) and Macrosomia (OR 0.62, 95% CI 0.18–2.11, $p = 0.44$, $I^2 = 57\%$).
  - *Neonatal hypoglycemia* The analysis of 671 patients from four studies [12, 13, 23, 24] did not show significant difference in neonatal hypoglycemia (OR 1.86, 95% CI 0.24–14.58, $p = 0.55$, $I^2 = 38\%$).
  - *NICU admission* Data from three studies [12, 13, 23] including 530 patients did not show difference in NICU admission among groups (OR 0.39, 95% CI 0.13–1.19, $p = 0.10$, $I^2 = 0\%$).

MYO vs no intervention

- Maternal health
  - *GDM rate* Analysis involved a total number of 608 patients ($n = 291$ receiving MYO and $n = 304$ controls) from three studies [12, 23, 24]. The overall results significantly favoured ISLs (OR 2.97, 95% CI 1.89–4.66, $p < 0.00{,}001$), with no heterogeneity across studies ($I^2 = 0\%$) (Fig. 1a)
  - *FG-OGTT, 1HG-OGTT and 2HG-OGTT* Three studies [12, 23, 24] with 614 participants were included ($n = 304$ receiving MYO and $n = 310$ Controls). A significant advantage was observed in MYO group concerning FG-OGTT (MD = − 3.15, [95% CI − 4.43, − 1.87], $p < 0.00001$, $I^2 = 0\%$), 1HG-OGTT (MD = − 9.86, [95% CI − 14.84, − 4.88], $p = 0.0001$, $I^2 = 17\%$) and 2HG-OGTT (MD = − 9.64, [95% CI − 17.72, − 1.55], $p = 0.02$, $I^2 = 73\%$) (Fig. 1b–d)
  - *Weight gain at OGTT* Data showed in the previous section (ISLs vs no intervention).
  - *Hypertensive disorders* A total number of 595 patients were analyzed from three studies [12, 23, 24]. No difference among groups was found (OR 0.40, 95% CI 0.07–2.26, $p = 0.30$, $I^2 = 43\%$) (Fig. 1e)
  - *Total cholesterol, LDL, HDL, triglycerides, SBP and DBP after 30/60 days* No study evaluated the metabolic changes associated with MYO administration alone.

- Delivery outcomes
  - *CS rate* The analysis of 595 patients ($n = 408$ in ISLs group and $n = 421$ controls) from four studies [12, 23, 24] did not show any difference in CS rate (OR 0.85, 95% CI 0.65–1.13, $p = 0.28$, $I^2 = 0\%$).
  - *Preterm delivery* Data from three studies [12, 23, 24] about 595 patients showed lower prevalence of preterm delivery in MYO group (OR 0.38, 95% CI 0.16–0.87, $p = 0.02$, $I^2 = 0\%$) (Fig. 1f)
  - *Shoulder dystocia* See the previous section (ISLs vs No Intervention).

- Feto-neonatal health
  - *GA at birth* Data from three studies [12, 23, 24] about 595 patients showed no significant difference in GA at birth among groups (MD = 0.74, [95% CI − 1.06, 2.64], $p = 0.42$, $I^2 = 0\%$).
  - *Birth weight and Macrosomia* The analysis of 595 patients from three studies [12, 23, 24] did not show significant difference in birth weight (MD = − 61.29, [95% CI − 177.81, 55.23], $p = 0.30$, $I^2 = 52\%$) and Macrosomia (OR 0.33, 95% CI 0.06–1.90, $p = 0.22$, $I^2 = 55\%$).
  - *Neonatal hypoglycemia* The analysis of 437 patients from three studies [12, 23, 24] did not show signifi-

cant difference in neonatal hypoglycemia (OR 0.53, 95% CI 0.05–5.22, $p=0.58$, $I^2=0\%$).
– *NICU admission* Data from two studies [12, 24] including 398 patients did not show difference in NICU admission among groups (OR 0.33, 95% CI 0.03–3.89, $p=0.22$, $I^2=34\%$).

MYO plus DCI vs no intervention

- Maternal health
  – *GDM rate, FG-OGTT, 1HG-OGTT, 2HG-OGTT, Weight gain at OGTT and hypertensive disorders* No difference was observed regarding GDM rate ($p=0.39$), FG-OGTT ($p=1.00$), 1HG-OGTT ($p=0.35$)and 2HG-OGTT ($p=0.13$), as well as in the percentage of hypertensive disorders ($p=0.11$) [13].
  – *Total cholesterol, LDL, HDL, triglycerides, SBP and DBP after 30/60 days* See the section "ISLs vs no intervention" (Fig. 1a–e).
- Delivery outcomes
  – *CS rate, shoulder dystocia, third degree perineal tear and preterm delivery* No difference was observed for all the outcomes evaluated (respectively, $p=0.66$, $p=0.11$, $p=0.34$ and shoulder dystocia) (Fig. 1f).
- Feto-neonatal health
  – *GA at birth, birth weight, macrosomia and NICU admission* No statistical difference was found among groups in all the outcomes evaluated (respectively $p=0.07$, $p=0.5$, $p=0.27$, $p=0.51$ and $p=0.56$).
  – *Neonatal hypoglycemia* Higher rate of hypoglycemia was observed in Intervention group in comparison to Controls ($p=0.01$).

Side effects associated with intervention

Among 411 patients receiving intervention (from all the studies included in the review [12, 13, 22–24]), no side effect was observed.

Overall quality of evidence

The overall quality of evidence was rated as very low for all the outcomes evaluated (Table 2).

The majority of studies were at high risk of reporting bias as well as at high risk of bias due to high inconsistency and small sample size (i.e. small number of patients and events). Moreover, publication bias due to "positive results" was strongly suspected.

Discussion

Main findings

Five RCTs were included, with a total number of 965 participants. Among 411 patients receiving intervention (MYO or MYO plus DCI), no side effect was reported.

ISLs supplementation was associated with lower rate of GDM, FG-OGTT values, total cholesterol, LDL, triglycerides and in a significant increase of HDL ($p<0.05$). Contrarily, no difference was observed in 1HG-OGTT, 2HG-OGTT, weight gain at OGTT, rate of hypertensive disorders, SBP and DBP ($p=$ ns).

Regarding the delivery outcomes, we observed lower preterm delivery rate in patients receiving ISLs ($p<0.05$), while no difference was found between groups in terms of CS rate, shoulder dystocia and third degree perineal tears ($p=$ ns). Finally, regarding feto-neonatal health outcomes, no difference among groups was observed in terms of GA at birth, birth weight, macrosomia, neonatal hypoglycemia, respiratory distress and NICU admission ($p=$ ns). The overall body of evidence was rated as very low (GRADE score 1).

The subgroup analysis based on the type of intervention (MYO 2 g twice daily versus MYO 1100 mg plus DCI 27.6 mg once daily) showed a significant advantage in terms of GDM rate, FG-OGTT, 1HG-OGTT, 2HG-OGTT and preterm delivery rate in patients receiving 2 g MYO twice per day. Contrarily, the daily administration of MYO (1100 mg) plus DCI (27.6 mg) did not show any benefit.

Limitations

To our knowledge, the present is the more comprehensive meta-analysis on this topic. However, our findings are primarily limited by the methodological flaws of the included studies. Moreover, the small sample size included in pooled analysis as well as patients' heterogeneity may represent additional sources of bias. Finally, the majority of studies were performed in Italy, potentially limiting the generalizability of our findings to other ethnic groups.

Implications and biological rationale of the intervention

In line with the trend toward older maternal age and rise of obesity, the prevalence of GDM has dramatically increased during the last 20 years [26, 27]. Because GDM is associated with high risk obstetric and perinatal complications, its spread must be considered as a major public health

Table 2 Evidence profile: inositol compared to no intervention for gestational diabetes prevention

Summary of findings						
Inositol compared to no intervention for gestational diabetes prevention						
Patient or population: Pregnant women at increased risk of gestational diabetes						
Setting: Not applicable						
Intervention: Inositol (myo-inositol alone or myo-inositol plus D-chiro inositol)						
Comparison: no intervention						
Outcomes	Anticipated absolute effects[A] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no intervention	Risk with inositol				
Gestational diabetes rate (GDM Rate)	227 per 1.000	126 per 1.000 (66–232)	OR 0.49 (0.24–1.03)	848 (4 RCTs)	⊕◯◯◯ Very low[a,b,c]	
Hypertensive disorders	45 per 1.000	15 per 1.000 (7–37)	OR 0.33 (0.14–0.82)	829 (4 RCTs)	⊕◯◯◯ Very low[a,c,d]	
Preterm delivery	69 per 1.000	25 per 1.000 (12–50)	OR 0.34 (0.16–0.71)	829 (4 RCTs)	⊕◯◯◯ Very low[a,c,d]	
Macrosomia	59 per 1.000	38 per 1.000 (11–118)	OR 0.62 (0.18–2.11)	829 (4 RCTs)	⊕◯◯◯ Very low[a,d,e]	
Cesarean section rate (CS rate)	416 per 1.000	380 per 1.000 (316–446)	OR 0.86 (0.65–1.13)	829 (4 RCTs)	⊕◯◯◯ Very low[a]	
Neonatal hypoglycemia	9 per 1.000	16 per 1.000 (2–113)	OR 1.86 (0.24–14.58)	671 (4 RCTs)	⊕◯◯◯ Very low[a,d]	
Neonatal intensive care unit admission (NICU admission)	34 per 1.000	17 per 1.000 (5–52)	OR 0.48 (0.15–1.57)	632 (3 RCTs)	⊕◯◯◯ Very low[a,d]	

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

CI confidence interval, *OR* Odds ratio

[A]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)

concern [28, 29]. Due to lack of safe and effective strategies in the prevention of GDM, the identification on novel targeted drugs is of critical importance [27–29].

ISLs are simple carbohydrates (belonging to vitamin B group) that play a pivotal role in the regulation of many hormonal and metabolic pathways in the human body [29, 30]. These molecules are ingested daily (as they are contained in different natural foods such as cereals, legumes and fruits) and their oral supplementation during pregnancy is unlikely to generate any appreciable health risk for mother and fetus [22, 24].

The most common stereoisomers of ISL, MYO and DCI mainly act as insulin-sensitizing agents [8]. Such effect is thought to be mainly related to the production of inositol glycan secondary messengers, with the enhancement of glycogen synthesis and glucose peripheral tissue uptake [5, 31]. Different insulin-mediated disorders [i.e., type II diabetes (T2D), polycystic ovarian syndrome (PCOS)] have been associated with an unbalanced MYO and DCI ratio, perhaps due to a reduced ISL epimerase activity (namely, a reduced conversion of MYO to DCI) [32–34]. Accordingly, studies on women with PCOS and T2D found a significant improvement in terms of insulin resistance after ISLs administration [35, 36]. These metabolic changes was accompained by the restoration of regular periods and higher reproductive chances in oligomenorrheic, infertile women [37, 38].

The positive effects of ISL on glucose homeostasis and metabolic functions in GDM may be due to comparable biological reasons to those discussed above. Our results are supported by a recent murine study (on pregnant mice) showing

that MYO administration was associated with adipose tissue markers of improved insulin sensitivity and glucose uptake [39]. Moreover, we must stress that all the RCTs included in our review found a certain benefit from ISLs, with the exception of the one by Farren et al. [13]. Such a discrepancy was potentially ascribable to the different molecules, dosages and regimens adopted in the trial by Farren et al. [13] in comparison to other studies [12, 22, 23] (1.1 g MYO plus 27.6 g DCI once daily in the study by Farren et [13] al versus 2 g MYO twice daily in other studies [12, 22, 23]). At this regard, Orrù et al. [40]. recently demonstrated that the half-life of ISLs is considerably short (near to 12 h), concluding that 2 g of MYO twice per day might be the preferable regimen to guarantee 24-h drug coverage.

Based on these premises, an adequate administration of ISLs may be beneficial for pregnant women at risk for GDM [22]. Nevertheless, further studies are needed to better elucidate the molecular mechanisms of action of ISLs.

Conclusions

ISLs administration during pregnancy appears to be safe and may represent a novel strategy for GDM prevention. In particular, the daily administration of MYO 2 g twice daily may improve the glycemic homeostasis and may reduce GDM rate and preterm delivery rate. Due to poor quality of evidence available, further robust and good-quality RCTs are still needed to confirm the effectiveness and optimal dose of ISLs for GDM prevention. Future studies in different settings will also assess the potential application of ISLs to other ethnic groups.

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Compliance with ethical standards

Conflict of interest Nothing to declare.

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