The Efficacy of Myo-Inositol Supplementation on the Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis of Published Randomized Controlled Trials

Original Article

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ABSTRACT

Introduction: The efficacy of Myo-inositol on gestational diabetes mellitus remains debatable. We conducted this systematic review and meta-analysis to synthesize evidence from published studies on the efficacy and the impact of Inositol for cutting the risk of gestational diabetes mellitus in pregnant women.

Materials and Methods: We followed the standard methods of the Cochrane Handbook of Systematic Reviews for interventions and the PRISMA statement guidelines 2020 when conducting and reporting this study. A computer literature search of PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials conducted from inception until January 2022. We selected randomized controlled trials (RCTs) assessing the efficacy of Inositol on the gestational diabetes mellitus in pregnant women, and all relevant outcomes were pooled in the meta-analysis using Review Manager Software**.**

Results: Seven RCTs were included in our study with only six RCTs included in the meta-analysis. The pooled risk ratio suggested that myo-inositol supplementation is associated with significantly reduced incidence of gestational diabetes [RR=0.67, CI 95% (0.40, 1.12)]. However, there was no significant difference between Inositol and control in gestational age at delivery (days) and cesarean delivery percentage as following respectively; [MD=1.11, CI 95%, (-0.10, 2.31), *P=0.07*], and [RR=0.93, CI 95%, (0.81, 1.07), *P=0.33*]. Also, Inositol decreased the incidence of gestational hypertension and preterm delivery as following; [RR=0.49, CI 95%, (0.29, 0.82), *P=0.006*], and [RR=0.48, CI 95%, (0.31, 0.75), *P=0.001*]. There was no significant difference between Inositol and control in terms of the incidence of macrosomia, NICU admission, shoulder dystocia, neonatal hypoglycemia, and birth weight as following respectively; [RR=0.91, CI 95%, (0.57, 1.45), *P=0.68*], [RR=0.45, CI 95%, (0.17, 1.22), *P=0.12*], [RR=0.63, CI 95%, (0.147, 2.72), *P=0.538*], [RR=0.916, CI 95%, (0.539, 1.6), *P=0.747*], and [MD=3.49, CI 95%, (-51.11, 58.09), *P=0.9*].

Conclusion: Myo-inositol supplementation has some ability to reduce the incidence of gestational diabetes, gestational hypertension, and preterm delivery in pregnant women.

Key Words: GDM, Myo-inositol, PREGNANCY.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a state of glucose intolerance that is recognized firstly during pregnancy. Unfortunately, GDM leads to an increase in the clinical risk for the woman and her offspring. GDM can affect the fetus by increasing the risk of shoulder dystocia and macrosomia. Also, GDM can affect the newborn by increasing the risk of respiratory distress syndrome, neonatal hypoglycemia, and childhood obesity. Not only the fetus and the newborn who can be affected, but there are also many Maternal risks including hypertensive disorders, cesarean delivery, and an increased risk of developing type 2 diabetes later in life.[1]

Inositol is a chemical compound that was discovered in 1936. Some studies classify Inositol as a part of the vitamin B complex, while others consider it as a pseudovitamin. It was thought to be a B vitamin as it was prevalent in the diet. Inositol is endogenously synthesized through the liver and kidneys. You can also find Inositol in many foods like whole grain, dried fruits, legumes, cereals, grain seeds, and meat. D-chiro-inositol and Myo-inositol are the two stereoisomers of Inositol. Both compounds have an essential role in regulating cholesterol levels and generally in controlling sugar and fat metabolism.[2]

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Myo-inositol supplements have shown efficacy for ovarian function improvement and also polycystic ovarian syndrome (PCOS). Recently, Myo-inositol and the combination of D-chiro-inositol have been reported to have a vital role in reducing GDM incidence in pregnant women, especially those at risks, such as women with PCOS and obese women. In our systematic review and meta-analysis, we aim to synthesize evidence from published studies on the efficacy and the impact of Inositol for cutting the risk of GDM in pregnant women.[3–5]

PATIENTS AND METHODS

Inclusion criteria

We followed the PRISMA recommendations for randomized trials while conducting our meta-analysis[6].

We included randomized controlled trials that examine the effect of Inositol alone or with other supplementation to prevent gestational diabetes.

Search strategy

We used relevant search terms to collect all eligible publications from PubMed, Cochrane library, Web of Science, and SCOPUS. The searching terms were as follows: mesoinositol, myoinositol, chiro-Inositol, chiro Inositol, Inositol, "Diabetes, Pregnancy-Induced," "Diabetes, Pregnancy Induced," "Pregnancy-Induced Diabetes," Gestational Diabetes," Diabetes Mellitus, Gestational," and "Gestational Diabetes Mellitus."

We included only randomized controlled trials which have available full text in English.

Risk of bias assessment

We utilized the Cochrane Handbook for Systematic Reviews of Interventions, Second Edition, to evaluate the quality of each research. We looked at how biases in selection and performance and detection and attrition biases influenced the methodological quality. We assigned letters to each criterion as follows: "+" indicates that the study met all criteria and had a low risk of bias; "?" indicates that the study met some criteria but had an unclear risk of bias; and "-" indicates that the study did not meet all criteria and had a high risk of bias[6].

Data collection

We extracted the following details from each study:

(1) the name of the first author and the publishing year of the article, (2) study design, (3) inclusion criteria, (5) Intervention group details, (6) Control group details, (7) results for each study, (8) age at baseline (9) pre-gestational Body Mass Index, (10) Nulliparous (%), (11) HOMA-IR at first trimester (h); (12) Family history of type 2 diabetes.

Statistical Analysis

We used Review Manager 5.4.0 and open meta-analyst software were to conduct this meta-analysis. We used a risk ratio or mean difference and a 95% confidence interval (CI) to describe the study's findings (Der Simonian and Laird 1986). We depended on Q tests and I2 statistics to determine the degree of heterogeneity. If the I2 is more than 50% and the *P-value* is less than 0.1, there is high variability. We used a random-effects model to reduce heterogeneity. When the *p-value* was more than 0.1, it was considered statistically significant. We could not do a subgroup analysis due to the low number of publications included. We used open meta-analyst software for the outcomes with zero events in both groups[7,8].

RESULTS

Data collection and characteristics of studies

We discovered 913 relevant studies in the databases we searched. We eliminated 892 publications based on our analysis of their abstracts and titles. Fourteen of the remaining 21 papers were deemed insufficient for publication. In the end, Seven research projects were engaged.[1-7] According to our criteria, six of them were included in our analysis (Fig. 1). Summary and baseline of included studies are shown in (Table 1 and Table 2).

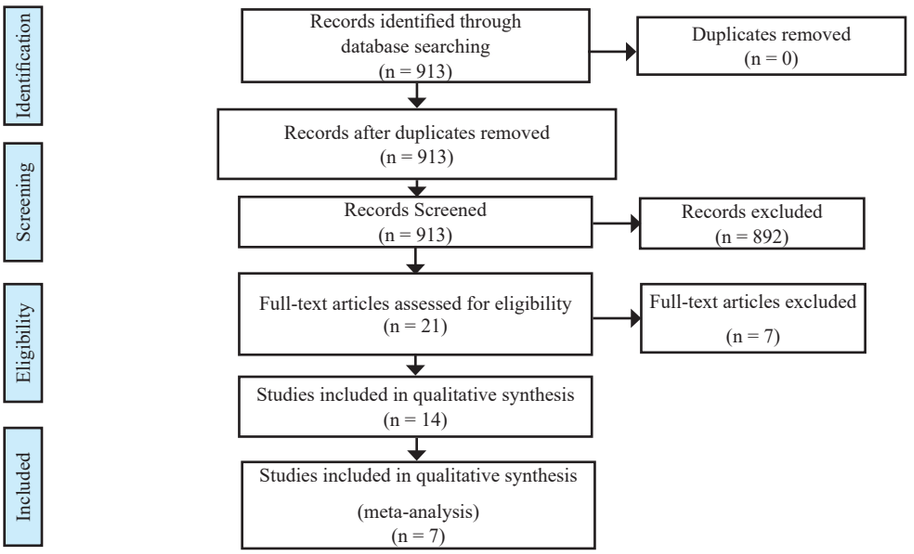


Fig. 1: Prisma flow diagram

Table 1: Summary of included studies.

Study ID	Site	Study design	Study arms and sample (reported results)	Inclusion criteria	intervention group	Control group	Result
Anna *et al*. 2013	Italy	Randomized controlled trial	197 Pregnant women, 99 in the myo-inositol group and 98 in the placebo group.	1) first-degree relatives (mother, father, or both) affected by type 2 diabetes, 2) prepregnancy BMI, 30 kg/m2, 3) fasting plasma glucose, 126 mg/dL and random glycemia, 200 mg/dL, 4) single pregnancy, and 5) Caucasian race.	2 g Myo-inositol was given twice a day plus 200 mg folic acid	Only 200 mg folic acid was given twice a day	"Myo-Inositol supplementation in pregnant women with a family history of type 2 diabetes may reduce GDM incidence and the delivery of macrosomic fetuses."
Anna *et al*. 2015	Italy	Randomized controlled trial	220 Pregnant women, 110 in the myo-inositol group and 110 in the placebo group.	1) prepregnancy body mass index (BMI) (calculated as weight (kg)/ [height (m)] 2) 30 or greater and 2) singleton gestation.	2 g Myo-inositol was given twice a day plus 200 mg folic acid	Only 200 mg folic acid was given twice a day	"Myo-inositol supplementation, started in the first trimester, in obese pregnant women seems to reduce the incidence in GDM through a reduction of insulin resistance."
Farren *et al*. 2017	Ireland	Randomized controlled trial	240 Pregnant women, 120 in the myo-inositol group and 120 in the placebo group.	"Women with a family history in a first-degree relative of diabetes, either type 1 or type 2, were eligible for inclusion."	Myo-Inositol 1,100 mg, D-chiro-inositol 27.6mg, and 400 mg folic acid per day	400 mg folic acid per day	"Commencing an inositol combination in early pregnancy did not prevent GDM in women with a family history of diabetes."

Godfrey *et al*. 2021	U.K., Singapore and New Zealand	Randomized controlled trial	575 Pregnant women, 295 in the myo-inositol group, and 290 in the placebo group.	"Women were eligible for trial enrollment if they were aged 18–38 years, were planning to conceive within six months and had future maternity care at the recruiting centers."	"Additionally adding the following to control 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]"	Folic acid 400 µg/day, iron 12 mg/day, calcium 150 mg/day, iodine 150 µg/day, and β-carotene 720 µg/day	"Supplementation with Myo-inositol, probiotics, and micronutrients preconception and in pregnancy did not lower gestational glycemia but did reduce preterm birth."
Malvasi *et al*. 2014	Italy	Randomized controlled trial	48 Pregnant women, 24 in the myo-inositol group and 24 in the placebo group.	1) Healthy pregnant women, 2) between the 13th and 24th week of gestation, 4) with a body mass index (BMI) between 25-30 (kg/m2), and 5) aged between 30 and 40 years.	2000 mg myo-inositol, 400 mg d-chiro-inositol, 400 µg folic acid, and 10 mg manganese.	Placebo	"Myo-inositol, D-chiro-inositol, folic acid an,d manganese administration after 30 days in pregnancy improved glycemic and lipidic parameters, with a significant gain after 60 days, without affecting diastolic blood pressure levels."
Santamaria *et al*. 2015	Italy	Randomized controlled trial	197 Pregnant women, 95 in the myo-inositol group and 102 in the placebo group.	1) pre-pregnancy BMI >25 and <30 kg/m2, 2) first-trimester fasting plasma glucose ≤126 mg/dl and/or random glycemia <200 mg/dl, 3) single pregnancy and 4) Caucasian ethnicity.	2 g Myo-inositol was given twice a day plus 200 mg folic acid	Only 200 mg folic acid was given twice a day	" Myo-inositol supplementation, administered since early pregnancy, reduces GDM incidence in overweight non-obese women."
Vitale *et al*. 2020	Italy	Randomized controlled trial	223 Pregnant women, 110 in the myo-inositol group and 113 in the placebo group.	1) pre-pregnancy BMI > 25 and < 30 kg/m2, 2) first-trimester fasting plasma glucose ≤126 mg/dl and/or random glycaemia <200 mg/dl, 3) single pregnancy, and 4) Caucasian ethnicity.	2 g Myo-inositol was given twice a day plus 200 mg folic acid	Only 200 mg folic acid was given twice a day	"This study results demonstrate the effectiveness of Myo-inositol supplementation in preventing GDM in overweight non-obese pregnant women."

Table 2: Baseline characteristics of included studies. Abbreviations; BMI: Body Mass Index, HOMA-IR: Homeostasis Model Assessment-Insulin Resistance index, NR: Not reported. Data marked by * is presented as median and ranges.

Study ID	Study arms	Sample	Age (M±SD)	pre-gestational BMI (M±SD)	Nulliparous (%)	HOMA-IR at first trimester (M±SD)	Family history of type 2 diabetes, n
Anna *et al*. 2013	Intervention	99	31.0 ± 5.3	22.8 ± 3.1	54.5	1.36 ± 0.7	NR
	Control	97	31.6 ± 5.6	23.6 ± 3.1	50	1.38 ± 0.8	NR
Anna *et al*. 2015	Intervention	110	30.9 (18–44)*	33.8 (30.0–46.9)*	47.3	3.0 ± 1.7	22
	Control	110	31.7 (19–43)*	33.8 (30.0–46.0)*	42.7	3.4 ± 3.7	41
Farren *et al*. 2017	Intervention	120	31.1 ± 5.1	26 ± 5.3	33	NR	10
	Control	120	31.5 ± 5	26.2 ± 5.5	32	NR	15
Godfrey *et al*. 2021	Intervention	295	30.53 ± 3.4	23.65 (21.16–26.23)*	58	NR	56
	Control	290	30.14 ± 3.3	23.75 (21.34–27.5)*	69	NR	79
Malvasi *et al*. 2014	Intervention	24	32.2 ± 5.46	26.98 ± 0.22	NR	NR	NR
	Control	24	31.58 ± 5.66	26.8 ± 0.22	NR	NR	NR
Santamaria *et al*. 2015	Intervention	95	32.1 ± 4.8	26.9 ± 1.3	51.6	2.18 ± 1.69	46
	Control	102	32.7 ± 5.3	27.1 ± 1.3	52.9	1.60 ± 1.08	34
Vitale *et al*. 2020	Intervention	110	27.18 ± 6.03	27.00 ± 1.49	46.36	1.96 ± 0.76	36
	Control	113	27.95 ± 4.90	26.68 ± 1.56	46.02	2.10 ± 0.77	42

Risk of bias assessment

Regarding selection bias, randomization in all studies was at low risk of bias except Farren *et al*. 2014, and Malvasi *et al*. 2014 were unclear. Also, all studies were low risk of bias at allocation concealment, except Anna *et al*. 2013 was unclear.

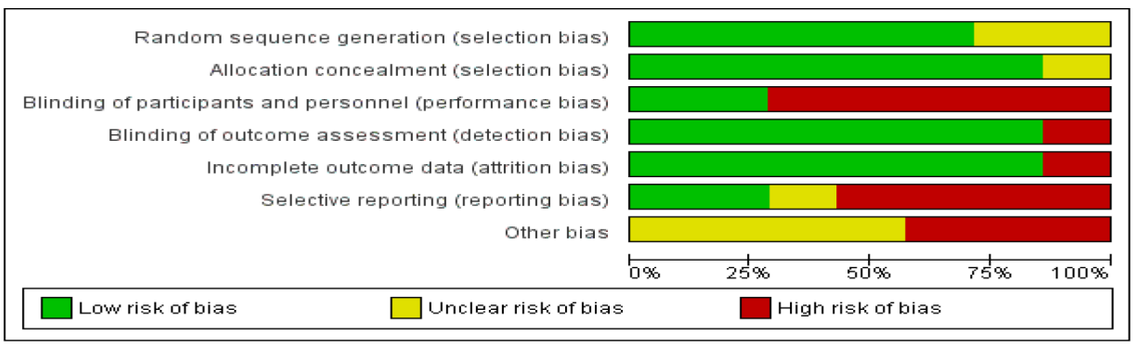
Regarding performance bias, in all studies, outcome assessors were blind except Vitale *et al*. 2020, an open-label study. Participants and personnel were blind in Godfrey *et al*. 2021 and Malvasi *et al*. 2014, and in the other studies were not blinded.

Regarding attrition bias, a small percentage of individuals dropped out in all trials except Malvasi *et al*. 2014 (26.1% of dropouts).

Regarding selective reporting, two studies were deemed to have a high risk of bias for selective data reporting due to the results being redesigned after protocol registration.[1,5] It was determined that the results of two further investigations were biased since no protocol registration was disclosed in the paper or discovered in registries.[2,6] It was unclear in Vitale *et al*. 2020.[7]

It was determined that all studies were either unclear or at high risk of bias. Farren *et al*. 2017 found a discrepancy between the pre-defined treatment and the final medication dosage (unclear risk of bias). While the proportion of patients who had previously been diagnosed with GDM was recorded in D' Anna *et al*. 2013, a non-comprehensive explanation of the techniques (i.e., timing/number of blood pressure measures) led to an unexplained bias in Malvasi *et al*. 2014. Finally, the other four studies may have been skewed because participants in the research had varying levels of acquaintance with type II diabetes.

The summary and graph of risk of bias are shown in Fig. 2 and Fig. 3.



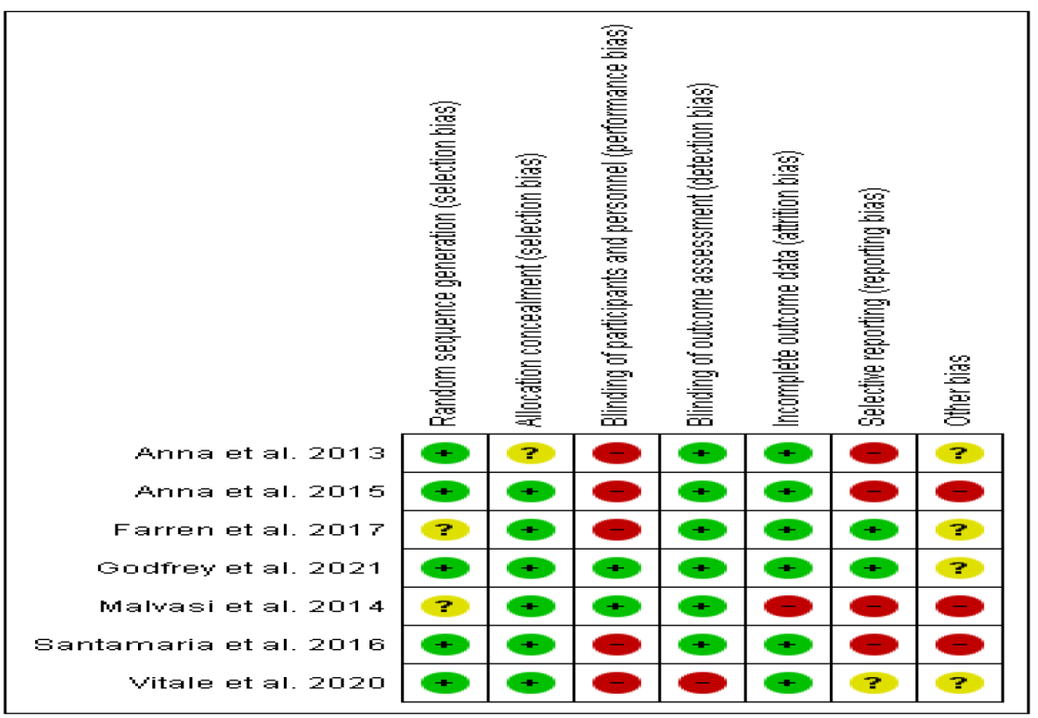


Fig. 2 and Fig. 3: The summary and graph of risk of bias are shown in

Meta-analysis results

Maternal outcomes

The pooled risk ratio suggested that myo-inositol supplementation is associated with significantly reduced incidence of gestational diabetes [RR=0.67, CI 95% (0.40, 1.12)] (Fig. 4). There was no significant difference between Inositol and control in gestational age at delivery (days) and cesarean delivery percentage as following respectively; [MD=1.11, CI 95%, (-0.10, 2.31), *P=0.07*], and [RR=0.93, CI 95%, (0.81, 1.07), *P=0.33*]. the data was homogenous in both outcomes as following respectively; [(*P = 0.50*), $I^2 = 0\%$], and [(*P = 0.95*), $I^2 = 0\%$] (Fig. 5 and Fig. 6).

Inositol decreased the incidence of gestational hypertension and preterm delivery as following; [RR=0.49, CI 95%, (0.29, 0.82), *P=0.006*], and [RR=0.48, CI 95%, (0.31, 0.75), *P=0.001*]. The data was homogenous in both groups as following; [(*P = 0.14*), I^2 = 42%], and [(*P = 0.59*), I^2 = 0%] (Fig. 7 and Fig. 8).

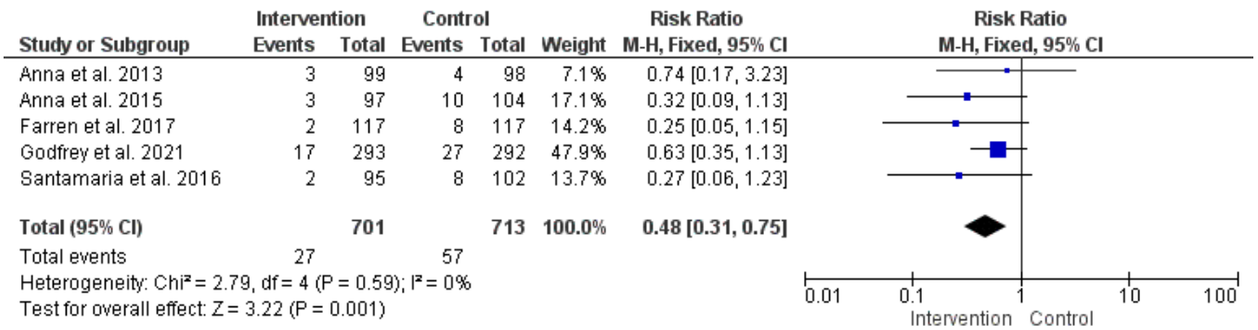
Neonatal outcomes

The incidence of macrosomia, NICU admission, shoulder dystocia, and neonatal hypoglycemia were as following respectively; [RR=0.91, CI 95%, (0.57, 1.45), *P=0.68*], [RR=0.45, CI 95%, (0.17, 1.22), *P=0.12*], [RR=0.63, CI 95%, (0.147, 2.72), *P=0.538*], and [RR=0.916, CI 95%, (0.539, 1.6), *P=0.747*], and the data was homogenous in all of them as following; [(*P = 0.11*), I^2 = 46%], [(*P = 0.40*), I^2 = 0%], [(*P = 0.949*), I^2 = 0%], and [(*P = 0.251*), I^2 = 0%] (Fig. 9 , Fig. 10, Fig. 11, and Fig. 12).

There was no significant difference between Inositol and control in Birth weight (g) as following; [MD=3.49, CI 95%, (-51.11, 58.09), *P=0.9*], but the data was heterogenous; [(*P = 0.02*), I^2 = 65%]. This heterogeneity was resolved by using random-effect model and excluding Anna *et al*. 2013, and the results remain insignificant as following; [MD=38.22, CI 95%, (-34.84, 111.28), *P=0.31*], and the data was homogenous; [(*P = 0.24*), I^2 = 28%] (Fig. 13).

Malvasi et al. 2014

The study was not included in the meta-analysis due to insufficient maternal and neonatal outcomes. They only reported no significant difference between Inositol and control regarding adverse events.



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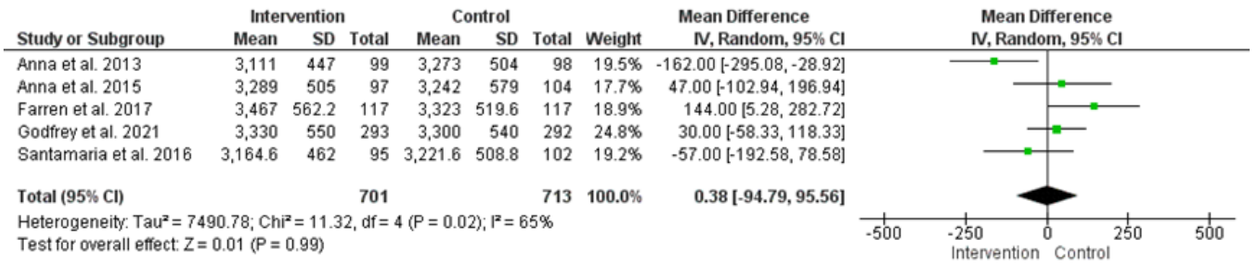

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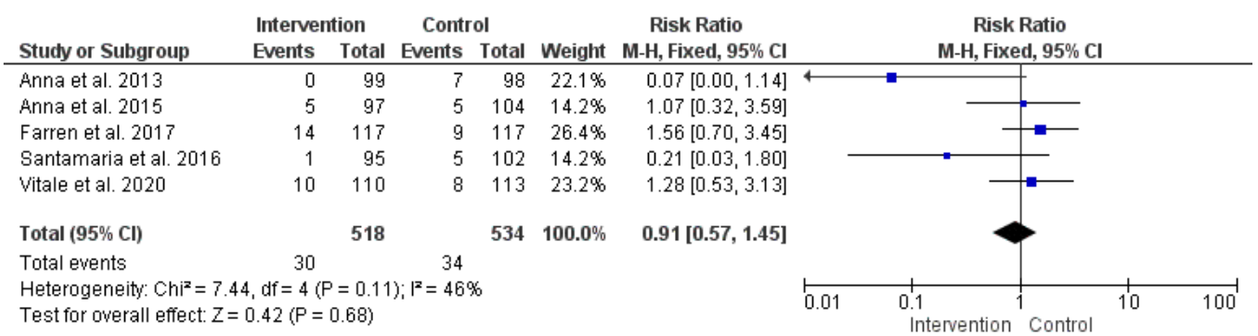

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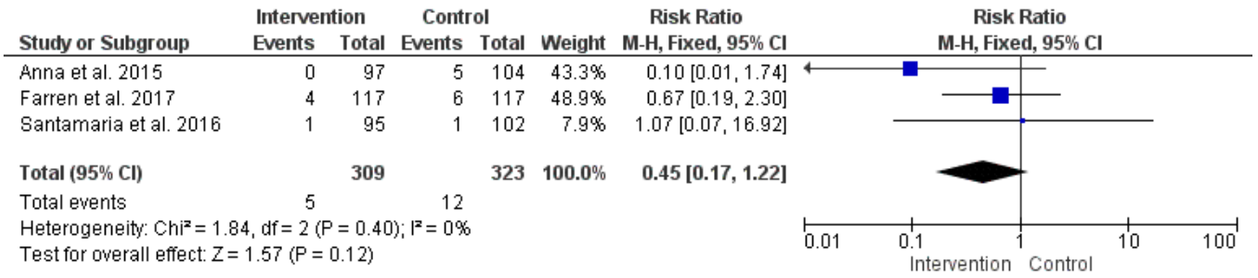

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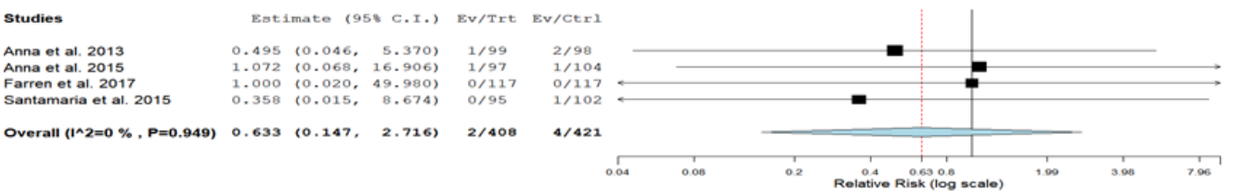

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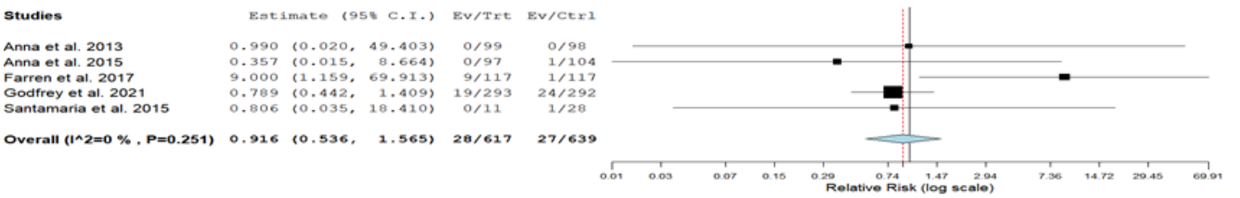

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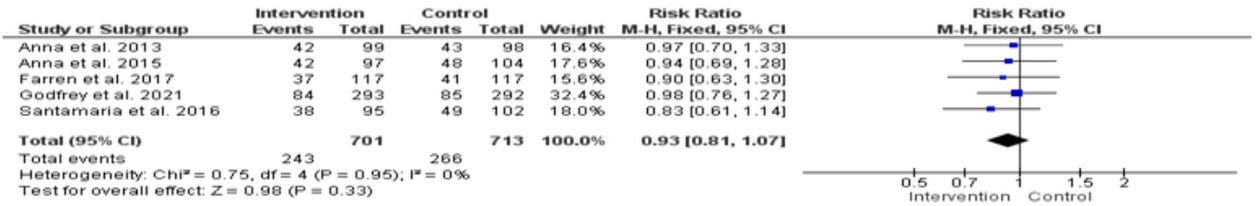

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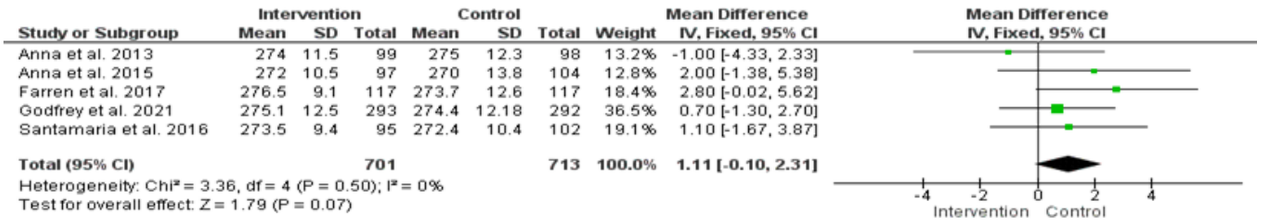

(Fig. 12)

DISCUSSION

Our systematic review includes seven RCTs. of them, six RCTs included in our meta-analysis. The results of our meta showed that Myo-inositol supplementation is associated with a significantly reduced incidence of gestational diabetes. Also, there is no significant difference between the inositol and control groups in terms of gestational age at delivery (days), cesarean delivery percentage, the incidence of macrosomia, NICU admission, shoulder dystocia, neonatal hypoglycemia, and birth weight. However, Inositol decreased the incidence of gestational hypertension and preterm delivery compared with placebo.

Agreements and disagreements with previous studies

Recently, the influence of Myo-inositol supplementation to prevent gestational diabetes onset has been widely debated. The results of our meta-analysis are in the same direction as the former meta-analysis conducted by Zheng *et al*. (XXX) in terms of the incidence of gestational diabetes mellitus and birth weight. They showed a significant reduction in aspects of gestational diabetes incidence in the group of patients who received Inositol compared with the placebo group. Also, they showed a significant reduction in the birth weight in the inositol group compared with the control which is consistent with our findings. Also, our study showed no significant difference between Inositol and control in birth weight, gestational age, and macrosomia which is coherent with the results reported by Gu *et al*.[16] and Zhang *et al*.[17]. Also, our results showed that Myo-inositol supplementation has some ability to reduce the incidence of gestational diabetes, gestational hypertension, and preterm delivery in pregnant women, which is consistent with Zhang *et al*.[17]. However, our study investigated the effect of Inositol compared with placebo on the incidence of NICU admission, shoulder dystocia, and neonatal hypoglycemia, which were not reported in these former meta-analyses.

Strength points and limitations

Our study has several strength points (1) we conducted all steps in strict accordance with the Cochrane Handbook of Systematic Reviews for interventions, (2) we followed the standard reporting guidelines of PRISMA statement to report this work, (3) we ran a comprehensive search of multiple electronic databases to identify all relevant studies, and finally (4) Our study reported class 1 evidence on the efficacy and the impact of Inositol for cutting the risk of GDM in pregnant women.

The beneficial effects of Myo-inositol supplementation on GDM appear promising. The optimal dose and the type of inositol isomer are still unclear, and the effects of different forms and various doses on GDM must be identified. Therefore, we recommend future well-designed, large RCTs to investigate the promising impact of different types of inositol isomer in a larger scale.

CONCOLUSION

Based on the current evidence, Myo-inositol reduces the incidence of GDM, although this conclusion requires further evaluation in large-scale, multicenter, double-blinded, randomized controlled trials.

CONFLICT OF INTEREST

There are no conflicts of interests.

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