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# Myoinositol supplementation in the prevention of gestational diabetes mellitus among high-risk pregnant women: A meta-analysis

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**Abstract:**

**OBJECTIVE:** The objective of the study was to determine the effectiveness of myoinositol (MI) supplementation in the prevention of gestational diabetes mellitus (GDM) among high-risk patients.

**MATERIALS AND METHODS:** Comprehensive and systemic online searches were performed on PubMed, MEDLINE, Ovid, and Cochrane. Cross-referencing from related articles was also done. Only studies published in English were included in the study. We selected all randomized controlled trials on MI and singleton pregnant women with high risk for GDM.

**DATA COLLECTION AND ANALYSIS:** Five randomized controlled trials were evaluated by two independent reviewers. For each comparison, the quality of evidence was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Cochrane Collaboration tool. Review Manager 5.3 was used to generate the risk of bias evaluation and the analysis of the results.

**MAIN RESULTS:** The present study identified five randomized controlled trials involving 871 participants. The comparison of the studies showed a statistically significant reduction in the incidence of GDM in MI supplementation versus the control group (odds ratio [OR] = 0.32, 95% confidence interval [CI] = 0.19–0.53, $P = 0.0001$, $Z = 4.36$) by 68%. Similarly, there is a greater reduction in the incidence of fetal macrosomia among patients in the MI group than the controlled group (OR = 0.24, 95% CI = 0.07–0.78; $P = 0.02$, $Z = 2.36$) by 78%. However, there was no difference in terms of incidence of gestational hypertension (OR = 0.61, 95% CI = 0.19–2.01; $P = 0.42$, $Z = -0.81$), cesarean section (OR = 0.89, 95% CI = 0.65–1.22; $P = 0.47$, $Z = 0.72$), and neonatal hypoglycemia (OR = 0.35, 95% CI = 0.01–8.80; $P = 0.53$, $Z = 0.63$) outcomes.

**CONCLUSION:** MI supplementation taken at 4 g daily would decrease the incidence of GDM and fetal macrosomia. There was no statistically significant reduction in the risk of gestational hypertension, cesarean section, and neonatal hypoglycemia in the supplementation of MI.

**Keywords:**

Cesarean section, fetal macrosomia, gestational diabetes mellitus, gestational hypertension, myoinositol, neonatal hypoglycemia

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## Introduction

Gestational diabetes mellitus (GDM) is defined as any form of glucose intolerance diagnosed during pregnancy.[1] It is the most common endocrine disorder during pregnancy, with a global and local prevalence of 7%–14% and 5%–29%, respectively, depending on the diagnostic criteria used, and considerable variability in different ethnic groups.[2,3] GDM causes several adverse maternal and neonatal complications such as hypertension in pregnancy, polyhydramnios, fetal macrosomia, and neonatal hypoglycemia, making it crucial for practical strategies for



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prevention. In women with a genetic predisposition to diabetes, GDM could be the first sign in the development of the disease.[4] Moreover, a preexisting history of overt diabetes or pregestational diabetes (nonmodifiable factor) and obesity (modifiable risk factor) markedly increases the risk for GDM. These factors lead to excessive glucose circulation to fetal blood, causing overnutrition and many other complications.[5] Several other risk factors, including advanced maternal age, ethnic background, and a family history of gestational diabetes, are linked to the development of GDM.[5] Therefore, screening and early diagnosis aid in timely intervention and prevention.

Prevention of gestational diabetes can also reduce the risk of type 2 diabetes in mothers and their children in the long term.[6] Several studies reported that insulin resistance or GDM usually resolves after delivery. However, based on prevalent data, a few years after diagnosis of gestational diabetes, approximately 50% still present with impaired glucose tolerance or progression to type 2 diabetes.[7]

Several strategies exist for managing GDM, including pharmacological and nonpharmacological measures. Currently, the recommended first step of management includes lifestyle and dietary modification. If the nonpharmacological intervention proves insufficient, administering oral antihyperglycemic agents or insulin is the next treatment option.[8] Recently, there has been an increasing number of interventional studies on potentially effective and safe supplements for high-risk pregnant women to prevent GDM or improve glucose homeostasis in those with preexisting diabetes.[9] One of which is the insulin-sensitizing property of inositol.

Myoinositol (MI), or inositol (cyclohexanehexol), is a cyclic carbohydrate with six hydroxyl groups.[10] It is one of the intracellular mediators of the insulin-signaling pathway and correlates with insulin sensitivity in type 2 diabetes mellitus. Production and activation of P13 kinase require MI for normal cell glucose metabolism.[10] Currently, investigators are gaining interest in the effectiveness of MI among women with GDM. MI is a dietary supplement that is taken orally and is used to treat insulin resistance. MI is reported to be inadequate in women with GDM. MI supplementation successfully prevents GDM by 65%–87% in high-risk women. A pilot study on the use of MI has shown a 75% reduction in the need for insulin for GDM not controlled by diet.[11] Existing and accessible meta-analyses and randomized studies on MI include small sample sizes. As such, the overall applicability of these findings could be clearer. Thus, the present research aims to update and summarize the available investigations.

## Objectives

### *General objective*

The general objective of the study was to determine the effectiveness of MI supplementation in the prevention of GDM among high-risk patients.

### *Specific objectives*

The specific objectives of the study were as follows:

1. To determine the incidence of maternal pregnancy complications among high-risk patients who develop GDM versus those who do not:
   a. GDM requiring pharmacologic treatment (insulin/metformin)
   b. Hypertensive disorders (pregnancy-induced hypertension and preeclampsia)
   c. Polyhydramnios
   d. Cesarean delivery
   e. Birth trauma.
2. To determine the incidence of neonatal outcomes among high-risk patients who develop versus those who do not develop GDM:
   a. Fetal macrosomia or large for gestational age
   b. Neonatal hypoglycemia.

# Materials and Methods

## Eligibility criteria

This study protocol was developed and executed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. All of the following inclusion criteria in PICOS order were set by the studies included in our meta-analysis [Table 1].

Articles with no assessment of the above outcomes, no comparison between two groups, duplicate reports, and conference abstracts were all excluded from the study. Retrospective trials, case reports, biochemical trials, letters, and reviews were also eliminated. Two independent authors screened the titles and abstracts of the relevant studies and determined their eligibility based on the criteria. Disagreements were resolved by discussion among all investigators.

## Search strategy

A systematic electronic literature search was conducted using MEDLINE, PubMed, WHO International Clinical Trials Registry Platform, Ovid MEDLINE In-Process,

**Table 1: Studies' criteria of inclusion**

| Criteria | Variables |
|---|---|
| Population (P) | Pregnant women, high risk for GDM |
| Intervention (I) | Group with myoinositol |
| Comparison (C) | Group with no treatment or placebo |
| Outcome (O) | Development of GDM, one or more maternal complications, one or more neonatal complications |

GDM: Gestational diabetes mellitus

ClincialTrials.gov, and other nonindexed citation databases and Cochrane Library electronic database. All identified randomized controlled trials published in English from January 2010 to the present (2022) that studied the effect of MI among high-risk pregnant women in preventing the development of GDM were included in the study. The citations were identified with the use of a combination of the following text words: "myo-inositol," "myo-inositol," "inositol," "gestational diabetes mellitus," "GDM," "fetal macrosomia," and "randomized." All studies that matched the terms set by the researchers were retrieved. Titles and research abstracts were reviewed individually. No restrictions for geography or location were applied. However, restrictions on the English language were applied to human subjects and published in English.

## Study selection

Study selection, quality assessment, and data extraction were made by the primary investigator and coauthor. The included studies were also evaluated by the two investigators independently.

# Results

## Description of studies

### *Results of the search*

Figure 1 demonstrates the flowchart of the search and selection results. Initially, 69 relevant articles were found (22 PubMed, 43 EBSCO, and 4 Cochrane articles from the databases). However, 27 articles were identified and removed due to duplication using EndNote software. Of the remaining 42 articles, 31 were removed in the first level of screening (the title and abstract review). In the second level of screening (the full-text review), 5 of the remaining 11 articles entered the meta-analysis stage of the research [Figure 1].

### *Included studies and interventions*

Table 2 shows the baseline characteristics of the eligible randomized controlled trials (RCTs) in the meta-analysis. They were published between 2013 and 2022, and the total sample size was 1250. These five eligible trials were conducted in parallel design (two open-label and three double-blind studies). MI doses were 2000 mg with 2 μg of folic acid twice daily. The participants in four studies were divided into the intervention group (receiving MI and folic acid twice a day) and the control group. Moreover, the participants in the research by Esmaeilzadeh *et al*. were divided into the intervention group (receiving the supplement once a day) and the control group.[1]

In the five studies presented here, all studies reported on the incidence of gestational diabetes by 2 hour glucose OGTT;[1,4,12-14] four studies reported on pharmacologic treatment among those with GDM,[1,4,12,13] four studies reported on rate of cesarean section,[1,4,12,14] and three studies reported on pregnancy-

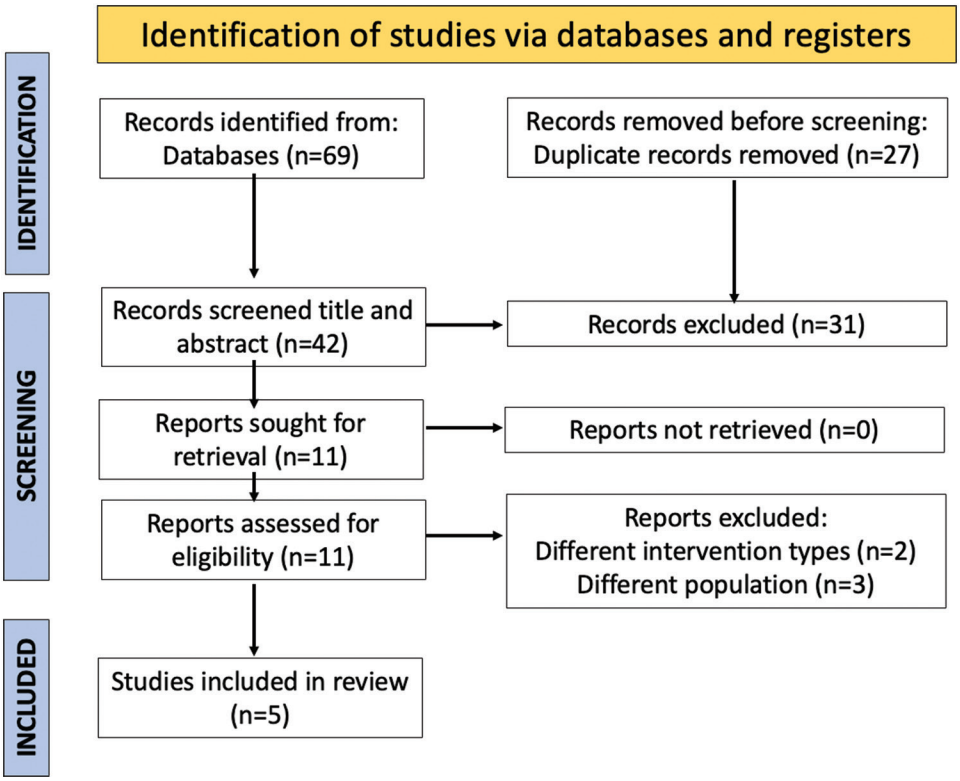


**Figure 1:** Flow diagram of study searching and selection process

**Table 2: Characteristics of included studies**

| Author, year | Design | Inclusion Criteria | MYOINOSITOL group | Placebo group | Participants | | Outcomes |
|---|---|---|---|---|---|---|---|
| | | | | | MI | PG | |
| Amaeule *et al*, 2022<br><br>UK (London and Manchester) | RCT<br>Multi-center | At least 16 years of age; singleton pregnancy between 12+0 to 15 + 6 weeks, | 2g myoinositol with 200 ug folic acid in a power form mixed in water BID | Xylitol filler with 200ug folic acid BID | 93 | 93 | Diagnosis of GDM at 28 weeks based on IADPSG criteria; Preeclampsia; Third/fourth degree tear; Large for gestation large (>90th percentile) |
| Esmaeilzadeh *et al*, 2018<br><br>Iran, Babol | RCT | Age 18-40 years, singleton pregnancy, overweight (pre pregnancy BMI ≥ 25 and < 30 kg/ m2)<br><br>14-16 weeks<br>Overweight | 2000 mg myo-inositol plus 200 mcg folic acid OD | 400mcg folic acid | 27 | 29 | Diagnosis of GDM at 24-28 weeks; Insulin therapy; Inappropriate gestational weight gain; Cesarean section; Preeclampsia; Fetal macrosomia; Should dystocia; neonatal respiratory distress syndrome; NICU admission |
| Santamaria *et al*, 2015<br><br>Italy, Messina | RCT | Pre-pregnancy BMI >25 and <30 kg/m2, first trimester fasting plasma glucose ≤ 126 mg/dL and/or random glycemia <200mg/dL, single pregnancy; Caucasia ethnicity<br><br>12-13 weeks<br>Overweight | 2g myo-inositol + 200 mcg folic acid BID | 200mcg folic acid | 95 | 102 | Occurrence of GDM; fetal macrosomia (>4g at delivery), rate of cesarean section, preterm delivery (<37 weeks), pregnancy induced hypertension, case of shoulder dystocia, neonatal hypoglycemia and neonates transferred to NICU |
| Vitale *et al*, 2020<br><br>Italy, Messina | RCT | BMI > 25kg/m2 and 30 <kg/m2 Overweight first trimester fasting plasma glucose < 126 mg/dl and/ or random glycaemia < 200 mg/dl<br><br>12-13 weeks<br>Overweight | 2g Myo-inositol + 200mcg folic acid BID | 200mcg folic acid | 110 | 113 | Occurrence of GDM, prevalence of fetal macrosomia, rate of cesarean sectionl preterm delivery, pregnancy induced hypertension, preeclampsia; should dystocia, neonatal hypoglycemia, NICU admission |
| D'Anna *et al*, 2013<br><br>Italy Messina | RCT | First degree relatives affected by type 2 DM, pre-pregnancy BMI <30kg/ m2, Fasting plasma glucose <126 mg/dL and Random glycemia <200 mg/dL; Single pregnancy; Caucasian race<br>12-13 weeks<br>Family history of DM | 2g myoinositol + 200mcg folic acid BID | 200mcg folic acid BID | 99 | 98 | Incidence of GDM, Fetal macrosomia (>4000g), cesarean section rate, gestational hypertension, preterm delivery, shoulder dystocia, neonatal hypoglycemia, respiratory distress syndrome |

induced hypertension.[1,12,14] Fetal secondary outcomes were reported as well. Three studies reported the incidence of fetal macrosomia,[1,12,14] two reported fetal hypoglycemia,[12,14] and one reported the gestational age at birth.[12] All included studies were regarded to have high quality because their Jadad scores varied from 3 to 5.

### *Participants*

Participants were from ages 27 to 32 years with a high risk for GDM. One of the five studies focused on women who previously had GDM, or who had previously given birth to a macrosomic baby (weighing more than 4.5 kg), or who had been identified as obese (BMI ≥ 30 kg/m$^2$) or with polycystic ovarian syndrome.[4] Four studies were conducted on overweight pregnant women,[1,12,13] while two were conducted on patients with a family history of diabetes.[4,14] Exclusion parameters included pre-GDM on maintenance with metformin or corticosteroids.

The gestational age at enrollment and the beginning of the intervention in pregnant women were 12–13 weeks in three studies[12-14] and 12–16 weeks in the two other studies.[1,4]

The duration of the intervention in four studies was until delivery.[1,4,12,14] In one study, it was until 3 weeks after delivery.[15]

### *Settings*

The geographical locations of the studies included London, Manchester, Iran, and Italy.

### *Outcome measures*

In all five studies, fasting glucose and 1-h and 2-h OGTT levels in the second trimester of pregnancy were measured at 24–28 weeks of gestation based on the diagnostic criteria by the American Diabetes Association or the International Association of the Diabetes and Pregnancy Study Groups, i.e. OGTT with 75 g of oral glucose. According to these criteria, if one of these values exceeded the determined limit, it would indicate GDM. Pregnancy outcomes, such as gestational hypertension and fetal macrosomia, were reported in three studies[1,12,14] and cesarean delivery and neonatal hypoglycemia[12,14] in two studies. Given the outcomes assessment, quantitative variables, such as fasting glucose and 1-h and 2-h OGTT levels, were reported as mean ± standard deviation separately for the groups. The qualitative variables, such as GDM rate and pregnancy outcomes, such as gestational hypertension, cesarean section, preterm delivery, macrosomia, shoulder dystocia, neonatal hypoglycemia, and neonatal intensive care unit admission, were reported in percentage and frequency in all studies.

### *Risk of bias in included studies*

The quality of the studies was high because only RCTs were included in the study. The risk of bias was assessed using the criteria provided in the PRISMA Cochrane Collaboration tool. It was generally low across all studies except for two studies with an unclear risk of blinding.

All the trials included were at low risk for selection bias through random-sequence generation and allocation concealment. The third domain, i.e. deviation from the intended intervention, had an unclear risk of bias in two studies,[12,13] with a high risk of bias in one.[14] The outcomes assessment was low risk in two studies[1,4] and unclear risk in three.[12-14] None of the studies had attrition and reporting bias [Figures 2 and 3].

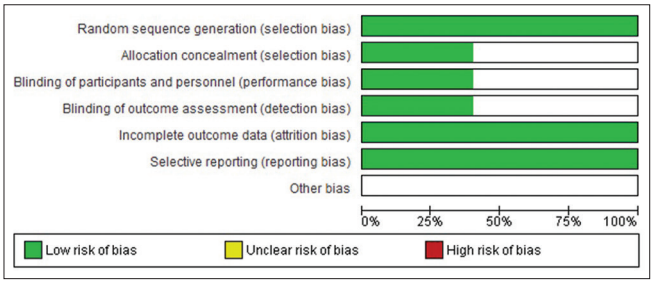


**Figure 2:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses graph. Flow diagram of the meta-analysis

## Outcome

### *Meta-analysis of included studies: Effects of interventions*

### Primary outcome: The incidence of gestational diabetes mellitus

Five RCTs reported the incidence of gestational diabetes, and the result found that MI supplementation was associated with a significantly reduced incidence of gestational diabetes by 68% than in the placebo group [Figure 4].

### Secondary outcomes

#### Gestational hypertension

Three studies with 450 participants evaluated the incidence of pregnancy-induced hypertension disorders. No difference in the incidence of hypertensive disorders was observed between MI supplementation compared to the control group [Figure 5].

#### Cesarean section

The overall results of the four trials with 648 participants showed no significant difference in cesarean section rates comparing MI supplementation to the control group [Figure 6].

#### Fetal macrosomia

The meta-analysis of three trials with 450 participants showed that the intervention group (MI) showed

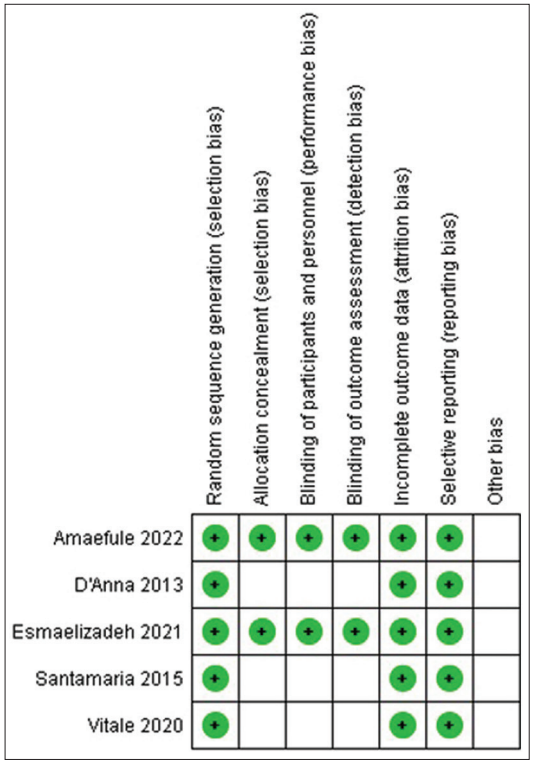


**Figure 3:** Risk of Bias Graph and Summary. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. Risk of bias summary: review authors' judgments about each risk of bias item for each included study

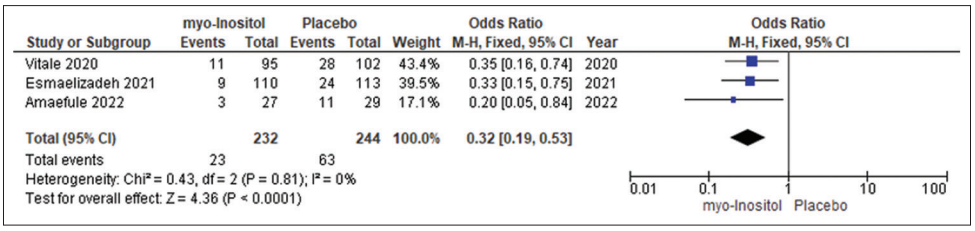


**Figure 4:** The resulting $I^2$ of 0% ($P$ = 0.81) implies heterogeneity does not exist and the fixed-effects model is preferred. The pooled odds ratio of 0.32 (95% confidence interval = 0.19–0.53) is statistically significant ($P$ = 0.0001, $Z$ = 4.36), implying that the intervention group (myoinositol) has significantly lower cases of gestational diabetes mellitus than the placebo group. CI: Confidence interval

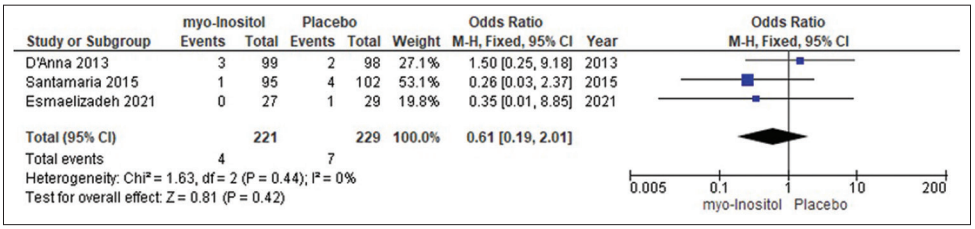


**Figure 5:** The resulting $I^2$ of 0% ($P$ = 0.44) implies heterogeneity does not exist and the fixed effects model is preferred. The pooled odds ratio of 0.61 (95% confidence interval: 0.19–2.01) is not statistically significant ($P$ = 0.42, $Z$ = 0.81), implying that the intervention group (myoinositol) has the same cases of hypertension as the placebo group. CI: Confidence interval

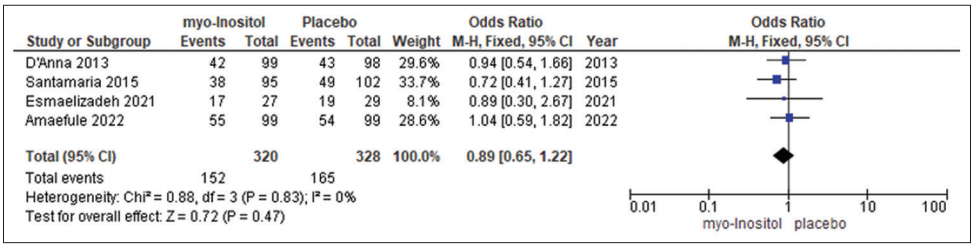


**Figure 6:** The resulting $I^2$ of 0% ($P$ = 0.83) implies heterogeneity does not exist and the fixed-effects model is preferred. The pooled odds ratio of 0.89 (95% confidence interval: 0.65–1.22) is not statistically significant ($P$ = 0.47, $Z$ = 0.72), implying that the intervention group (myoinositol) has the same cases of cesarean section as the placebo group. CI: Confidence interval

a significant 78% decrease in the incidence of fetal macrosomia than the placebo group [Figure 7].

### Neonatal hypoglycemia

Two studies, with 395 participants, evaluated the incidence of neonatal hypoglycemia. No difference in the incidence of neonatal hypoglycemia was observed between MI supplementation compared to the control group [Figure 8].

## Discussion

Pregnancy causes physiological hyperinsulinemia and insulin resistance to promote fetal growth and meet maternal metabolic demands. GDM is a pathologic type of glucose intolerance characterized by hyperglycemia and oxidative stress-related inflammation diagnosed during pregnancy. These can alter intracellular signaling pathways, including insulin signaling pathways leading to insulin resistance and decreased insulin gene expression, thus resulting in reduced insulin secretion by beta-pancreatic cells.[2] Several short- and long-term complications of GDM for both mother and fetus highlight the significance of identifying the risk factors for this metabolic disorder. Being overweight, obese, and having a preexisting history of overt or pre-GDM are among the most common risk factors for GDM. Other risk factors for GDM development include advanced maternal age, ethnic background, and a family history of gestational diabetes.[3] These risk factors may lead to intensified insulin resistance during pregnancy. With the increased incidence of GDM in recent years, clinical trials and observational studies have focused on noninvasive treatment and prevention (diet and nutritional supplementation).

MI, a stereoisomer of inositol, is used as a precursor of various secondary messengers, especially inositol triphosphates, phosphatidylinositol phosphate lipids, and inositol glycans. It can affect metabolic enzymes in glucose metabolism similar to that of insulin; hence, it is natural to consider inositol as an effective insulin sensitizer to prevent GDM, the primary pathophysiological mechanism of which is believed to be insulin resistance.[9,10] Two recent meta-analyses (five studies with 965 pregnant women and four studies with 567 pregnant women) who were at risk for GDM showed that taking MI significantly reduced the risk of GDM

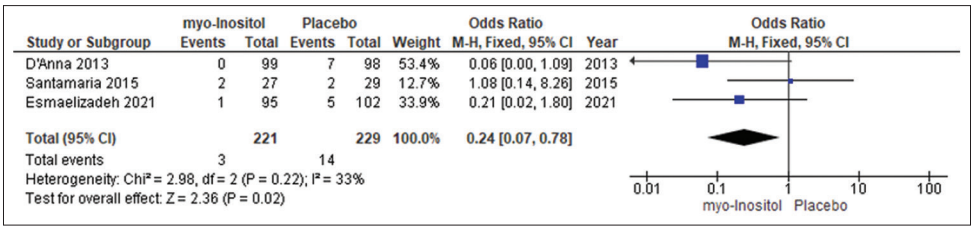


**Figure 7:** The resulting $I^2$ of 33% ($P$ = 0.22) implies heterogeneity does not exist and a fixed-effects model is preferred. The pooled odds ratio of 0.24 (95% confidence interval: 0.07–0.78) is statistically significant ($P$ = 0.02, $Z$ = 2.36), implying that the intervention group (myoinositol) has significantly lower cases of fetal macrosomia than the placebo group. CI: Confidence interval

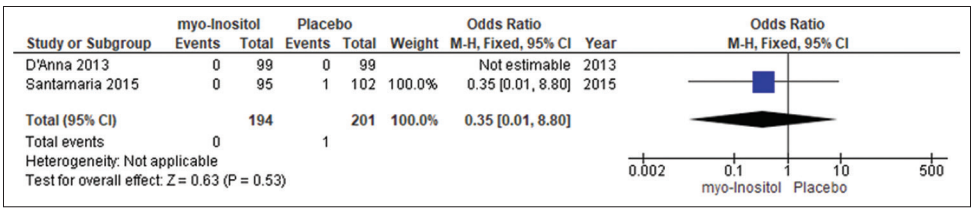


**Figure 8:** The resulting pooled odds ratio of 0.35 (95% confidence interval: 0.01–8.80) is not statistically significant ($P$ = 0.53, $Z$ = 0.63), implying that the intervention group (myoinositol) has the same cases of neonatal hypoglycemia as the placebo group. CI: Confidence interval

and fasting glucose based on OGTT.[16,17] The research above has included women diagnosed with GDM during pregnancy.

The previous meta-analysis focused on MI supplementation's effects in preventing gestational GDM among nonhigh-risk pregnant women.[12,13] However, the presented meta-analysis has included existing randomized controlled trials with the intervention of MI supplementation among pregnant women with high risk for the development of GDM. The primary finding is consistent with previous investigations in 2015 (Zheng's meta-analysis of five trials involving 513 pregnant women with GDM and Crawford's study on four problems involving 567 pregnant women), both of which used varying doses of MI alone or in combination with other materials.[14,18] However, in a meta-analysis of Vitagliano, the use of higher doses of MI showed a significant effect on the incidence of GDM, fasting glucose, and 1-h and 2-h OGTT levels. This study's findings are all from RCTs published through December 2022 on pregnant patients at high risk of developing GDM who received an intervention of 4 g of MI/day (2 g twice a day).[19] This supports the biochemical mechanism hypothesis by which MI improves the metabolic status of women by acting as an insulin-sensitizing agent, thereby increasing glycogen synthesis and glucose uptake in peripheral tissues.[20]

The present study evaluated the secondary outcomes, including pregnancy-induced hypertension, cesarean section, fetal macrosomia, and neonatal hypoglycemia. Three RCTs reported the incidence of fetal macrosomia among those who had GDM, and the result found that MI supplementation was associated with significantly reduced cases of fetal macrosomia.[1,21,22] This shows that maternal glycemic control is associated with fetal growth patterns.

Other secondary outcomes revealed no significant difference between MI supplementation and control groups. Some evidence suggests that MI affects vascular endothelial function as well. A recent systematic review showed that inositol supplementation significantly reduces systolic and diastolic blood pressure.[23] However, in the present study, this effect was not evident and may be attributed to a chronic vascular dysfunction beyond the intervention's duration and scope. Several other factors may also be considered regarding the cesarean section rates. Indications of the cesarean section may not always be due to a fetopelvic disproportion secondary to poor glycemic control; however, indications for the cesarean section were not reported in the RCTs. Finally, pregnant women may have different conditions, risks for infection, weight gain, etc., which result in different risk levels of GDM and influence the assessment of neonatal hypoglycemic status.

The strength of this research is that it was conducted specifically on the effect of MI on the prevention of GDM in high-risk pregnant women. One of its limitations is the small sample size, with only five clinical trials included. More RCTs are needed to improve study outcomes. Another limitation is that three of the five studies were conducted in Italy. Further, studies are required in different countries and ethnic groups to enhance the generalizability of our findings. It is recommended that clinical trials be performed in various settings with sufficient sample size, statistical power, and quality to increase the generalizability of their findings to other populations.

## Conclusion

The meta-analysis revealed that MI supplementation significantly reduced the incidence of GDM in pregnant women with a high risk for this condition. There was a statistically significant reduction in the incidence of fetal macrosomia among patients on MI supplementation. There was no significant difference between MI supplementation versus control in decreasing the incidence of gestational hypertension, cesarean section, and neonatal hypoglycemia. Further, studies are required to determine the efficacy of MI supplementation in preventing GDM among those at high risk of developing the disease.

### Authorship contribution

Ong, Ava - involved in the conceptualization, methodology, data curation, writing of the original draft, review and editing.

Songco, Debby - involved in conceptualization, methodology, review and editing of the draft.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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