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Myoinositol supplementation for the prevention of gestational diabetes in at-risk patients. Systematic review and meta-analysis



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ABSTRACT

Background: Gestational diabetes (GD) is associated with an increase in maternal and fetal morbidity. The risk factors involved have been clearly identified but no prevention strategies have yet provided robust evidence of their efficacy. Myoinositol has insulin sensitization properties and is of potential interest in the treatment of the disorder.

Aim: The aim of this work was to assess the efficacy of myoinositol supplementation during pregnancy to prevent GD in patients with known risk factors.

Method: A systematic literature review was performed on studies comparing the effects of myoinositol supplementation and placebo on the occurrence of GD in at-risk pregnant women. The main judgement criterion was diagnosis of GD between 24 and 28 gestational weeks by an oral glucose tolerance test. The secondary judgement criteria were the occurrence of maternal fetal complications and the need to initiate insulin treatment to manage GD.

Results: Nine studies were included in the meta-analysis. The results showed a significantly higher risk of GD in patients on placebo than in those receiving myoinositol (RR = 2.58, CI 95%: 1.68 to 3.97, $p < 0.0001$) but wide variations between studies ($I^2 = 71.94\%$, $p < 0.001$). And the risk of prematurity was significantly greater in the children of mothers on placebo (RR: 2.15, IC 95%: 1.32 to 3.20, $p = 0.002$).

Conclusion: Myoinositol supplementation taken from the beginning of pregnancy reduces the incidence of GD and could be of interest at a dose of 4 g/day as a prevention strategy for patients with identified risk factors.

1. Introduction

1.1. Rationale

Gestational diabetes (GD) is one of the commonest complications of pregnancy. Its incidence is currently rising in France and worldwide, notably due to increased obesity in the general population and advanced maternal age at conception. The condition is the cause of numerous neonatal and fetal complications both in the short term and several years after its occurrence. For these reasons, GD has become a major challenge in terms of public health.

Although the risk factors of GD have been clearly established no prevention strategy has given sufficient evidence of its efficacy to be

recommended in the management of patients at risk of developing the disorder.

Numerous studies of new prevention strategies with or without drugs are in progress. A recent overview of Cochrane reviews provided an update of our current knowledge (Griffith et al., 2020). Certain strategies have potential benefit but in most cases there is not sufficient robust evidence to assess their relative merits. Consequently, there are no consensual guidelines on how to prevent GD. Approaches adopted so far are based on dietary measures, physical activity, or a combination of the two, treatment with metformin, and dietary supplements of vitamin D, probiotics, omega-3 fatty acid or myoinositol. Supplementation with myoinositol, which is an isomer of inositol found naturally in food, is a promising strategy. Myoinositol, which has been widely studied in recent

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years, is a precursor of phosphatidylinositol and inositol phosphates and is thought to be involved in insulin sensitivity and oocyte maturation. It is available as a dietary supplement in the form of water soluble powder or capsules. According to a meta-analysis published in 2011 (Carlomagno and Unfer, 2011), the adverse effects of myoinositol treatment appear at doses of 12 g/day or above. No side effects were observed at doses of 4 g/day, which is the dose most commonly used in clinical practice. The mode of action of myoinositol and its derivatives via their different signalling pathways has been only partially elucidated, and further studies are needed to determine the intermediate mechanisms that contribute to their physiological effects (Croze and Soulage, 2013).

Numerous studies in the last few years have investigated the physiological role of myoinositol and its clinical and therapeutic potential (Larner, 2002; Baillargeon et al., 2008; Wojciechowska et al., 2019). By improving sensitivity to insulin, supplementation with myoinositol could be useful as a prevention strategy for patients at risk of GD.

1.2. Objectives

The objectives of this systematic review were to study of myoinositol effects in the prevention of GD occurrence in at-risk patients. The incidence of GD was diagnosed by an oral glucose tolerance test (OGTT) between 24 and 28 gestational week (GW).

2. Materials and methods

This work consisted in a systematic literature review of myoinositol supplementation in pregnant women and a meta-analysis of studies reporting its effect on the prevention of GD.

Ethical approval and patient consent were not required since the work was based on previously published studies. The meta-analysis was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations (Moher et al., 2010).

• Research strategy and study selection

In November 2021, two independent investigators working independently began searching the databases of Pubmed, Embase, Science-Direct et Cochrane using the keywords “inositol” and “gestational diabetes”. The bibliography of the full-text studies selected was also reviewed to identify potentially relevant publications. The inclusion criteria were pregnant women known to be at risk of developing GD who were receiving either myoinisitol supplementation combined with folic acid (FA) or FA alone (400 µg/day). Exclusion criteria were pregnant patients with GD established at the initiation of myoinisitol supplementation. Potentially eligible publications were initially selected on the basis of the title and the abstract. The full text of eligible studies was then read to determine which should be included in the meta-analysis. At this stage, the exclusion criteria were noted.

• Data collection and outcome measures

Data from the studies selected for the meta-analysis were extracted using an Excel® spreadsheet. The following information was collected for each article: study characteristics (authors, country, number of centres, type of study, study design and setting, study period), participants characteristics (number of patients, age, body mass index, main inclusion criteria), type of intervention (drugs, doses, mode of administration), comparison criteria (GD incidence and main maternal fetal complications of GD) and study results.

The main judgement criterion for the meta-analysis was the incidence of GD diagnosed between 24 and 28 gestational weeks (GW) by an oral glucose tolerance test (OGTT) (75g). The secondary judgement criteria were the main maternal fetal complications of GD: prematurity (birth <37 GW), macrosomia (>4000g), cesarean section (CS), gestational

arterial hypertension or pre-eclampsia and neonatal hypoglycemia. A study was also made of how often insulin treatment was needed to manage GD.

• Assessment of study quality and risk of bias

The quality of the randomized controlled trials included was assessed by the modified Jadad scale (Jadad et al. 1996) based on the following three features: randomization (0–2 points), masking (0–2 points), and patient withdrawals and dropouts (0–1 point). The scores range from 0 to 5 points. A publication with a score lower than or equal to 2 is considered to be of low quality and a publication having a score greater than or equal to 3 to be of good quality. The risk of bias was assessed by the Cochrane tool of risk of bias for randomized controlled trials (Higgins et al., 2011). Seven items relating to the risk of bias were evaluated for each of the articles included:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other bias
- Statistical analysis

The meta-analysis took account of between- and within-study variability. As primary (incidence of gestational diabetes) and secondary endpoints were dichotomous, results were expressed with risk ratios (RR). To address the non-independence of data due to study effect, random-effects models (DerSimonian and Laird, 2015) were preferred to the usual statistical tests to assess RR with 95% confidence interval (CI 95%). Heterogeneity in the study results was assessed by forest plots and the I^2 statistic, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. I^2 values range between 0% and 100% and are typically considered low for 25%, modest for 25%–50%, and high for 50% (Higgins et al., 2003). Publication bias was assessed by funnel plots, confidence intervals and with the Egger regression test as formal statistical test. To check the robustness of the results, sensitivity analyses were performed which excluded studies that were not evenly distributed around the base of the funnel plots. A subgroup analysis was also performed for the primary endpoint to assess the specific effects of the different doses of myoinositol used in the interventions. Statistical analyses were performed with Stata software (version 15, StataCorp, College Station, TX). Two-sided type I error was fixed at 5%.

3. Results

• Literature search and study selection

The search of the databases in the literature identified an initial 339 potentially relevant articles (Fig. 1). After elimination of duplicates, the title and abstracts of the remaining publications were reviewed and 13 articles finally selected. Of these 13, 3 were discarded after reading of the full text showed they did not meet the inclusion criteria (Fraticegli et al., 2018; Corrado et al., 2011; Malvasi et al., 2017) and 1 other study was dismissed because of the lack of data available on the main judgement criterion (Facchinetti et al., 2013). A total of nine studies fulfilling the inclusion criteria were included in the meta-analysis (Celentano et al., 2020; Vitale et al., 2021; D'Anna et al., 2012; D'Anna et al., 2015; D'Anna et al., 2013; Matarrelli et al., 2013; Santamaria et al., 2016; Farren et al., 2017; Dell'Edera et al., 2017). All the studies were randomized controlled trials except for that of D'Anna R. et al. published in 2012, which was a retrospective study (D'Anna et al., 2012).

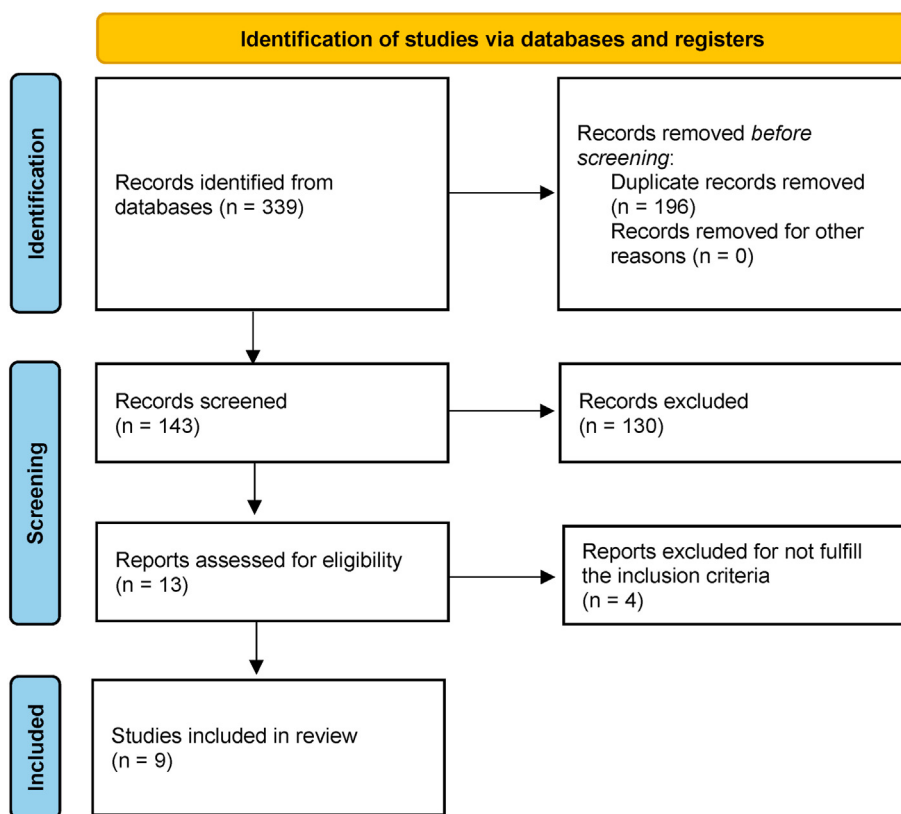


Fig. 1. Flow chart.

- Evaluation of study quality and risk of bias

The Jadad scores for the seven randomized controlled trials selected ranged from 3 to 5. All of the studies used an appropriate method of randomization and provided information on treatment cessation and patient withdrawals and dropouts. However, they did not apply blinding, but because of their score on the Jadad scale were considered to be of good quality.

Selection bias: All but one of the studies (Dell'Edera et al., 2017), which did not supply clear information, used an appropriate method of randomization (computer-generated random sequence). In one study (D'Anna et al., 2013), the method of attribution was not stated (uncertain risk of bias) but in all the others the method was appropriate (central or sealed envelopes).

Performance bias: Neither the personnel nor the participants were blinded in any of the studies, which results in a high risk of bias.

Detection bias: It is unlikely that the results assessed were affected by the fact that the studies were open. They were therefore considered to be at a low risk of bias.

Attrition bias: In all the studies there was a small patient dropout. According to Cochrane guidelines (Higgins et al., 2011), a dropout rate not exceeding 20% should not result in significant bias, which was the case in all the studies.

Reporting bias: Three studies were considered to be at high risk of bias in the selective report of data, two studies with modification of the judgement criteria after registration of the protocol (D'Anna et al., 2015; Santamaria et al., 2016) and one because no mention in the full text was made of the protocol being registered (D'Anna et al., 2013).

Other biases: In two studies there were notable differences between the intervention group and the group of controls in the existence of a family history of type 2 diabetes (D'Anna et al., 2015; Santamaria et al., 2016), which, since it is a recognised risk factor of the disease, could have affected the estimated outcome.

Finally, in the study of Farren et al. (2017), a difference was observed between the intervention in the pre-established protocol and the actual intervention in terms of drug regimens, which also leads to a risk of bias.

- Study characteristics

The nine studies involved a total number of 1546 patients. The baseline characteristics of the studies included in the meta-analysis are given in Table 1. The articles were published between 2012 and 2020 and patient sample sizes ranged from 84 to 250. All the articles assessed myoinositol supplementation in combination with FA supplements systematically recommended at the beginning of pregnancy. In six of the studies included, myoinositol was administered at doses of 4000 mg daily with 400 µg of folic acid (Vitale et al., 2021; D'Anna et al., 2012; D'Anna et al., 2015; D'Anna et al., 2013; Matarrelli et al., 2013; Santamaria et al., 2016). In one of the remaining studies, myoinositol was given at a daily dose of 1100 mg in combination with 27.6 mg of 1D-*chiro*-inositol and 400 µg of FA (Farren et al., 2017) while another reported the daily combination of 1700 mg of myoinositol, 250 mg of 1D-*chiro*-inositol, 12.5 mg of zinc, 10 mg of methylsulfonylmethane and 400 µg of FA (23). In the last study, two groups of patients were administered different dosages: 2000 mg twice a day of myoinositol with 400 µg of FA in the first group, and 1100 mg/day of myoinositol plus 27.6 mg of 1D-*chiro*-inositol and 400 µg of FA once per day for the second group (Celentano et al., 2020).

All the studies involved women identified as being at risk of developing GD, one on patients with polycystic ovary syndrome (PCOS) (D'Anna et al., 2012), two on patients with a family history of type 2 diabetes in first degree relative (D'Anna et al., 2013; Farren et al., 2017), three on patients who were overweight or obese before becoming pregnant (Vitale et al., 2021; D'Anna et al., 2015; Santamaria et al., 2016), and the final three on patients with a glucose tolerance disorder during the first trimester of pregnancy (Celentano et al., 2020; Matarrelli et al.,

Table 1
Characteristics of the studies included in the meta-analysis.

Studies	Jadad score (/5)	MYOINOSITOL group				Control group			
		Number (n)	Age (years (mean ± SD or (extrem values)))	BMI (kg/m ² (mean ± SD or (extrem values)))	Intervention	Number (n)	Age (years (mean ± SD or (extrem values)))	BMI (kg/m ² (mean ± SD or (extrem values)))	Intervention
<i>D'Anna R 2012</i> (D'Anna et al., 2012)	1	44	29.2 ± 3.8	26.2 ± 5.8	MYO 2g + FA 200 µg 2/day	54	30.6 ± 4.2	24.7 ± 3.9	FA 200 µg 2/day
<i>D'Anna R 2013</i> (D'Anna et al., 2013)	3	110	31.0 ± 5.3	22.8 ± 3.1	MYO 2g + FA 200 µg 2/day	110	31.6 ± 5.6	23.6 ± 3.1	FA 200 µg 2/day
<i>Matarrelli 2013</i> (Matarrelli et al., 2013)	3	39	33.0 ± 4.9	23.5 ± 3.4	MYO 2g + FA 200 µg 2/day	36	33.8 ± 4.7	24.7 ± 4.2	FA 200 µg 2/day
<i>D'Anna R 2015</i> (D'Anna et al., 2015)	3	110	31.9 (18-44)	33.8 (30.0-46.9)	MYO 2g + FA 200 µg 2/day	110	31.7 (19-43)	33.8 (30.0-46.0)	FA 200 µg 2/day
<i>Santamaria et al., 2016</i> (Santamaria et al., 2016)	3	110	32.1 ± 4.8	26.9 ± 1.3	MYO 2g + FA 20 µg 2/day	110	32.7 ± 5.3	27.1 ± 1.3	FA 200 µg 2/day
<i>Farren et al., 2017</i> (Farren et al., 2017)	3	120	31.1 ± 5.1	26.0 ± 5.3	MYO 1100 mg + DCI 27.6 mg + FA 400 µg 1/day	120	31.5 ± 5.0	26.2 ± 5.5	FA 400 µg 1/day
<i>D'ell'Edera 2017</i> (Dell'Edera et al., 2017)	2	43	32.5 ± 3.6	25.6 ± 4.0	MYO 1750 mg + DCI 250 mg + zinc 12,5 mg + methylsulfonylmethane 1/day	40	32.3 ± 3.8	26.9 ± 3.1	FA 400 µg 1/day
<i>Celentano et al., 2020</i> (Celentano et al., 2020)	3	60	33.1 ± 4.9	23.5 ± 3.4	MYO 2g + FA 200 µg 2/day	40	33.9 ± 4.9	24.4 ± 4.1	FA 200 µg 2/day
<i>Vitale 2020</i> (Vitale et al., 2021)	3	125	27.8 ± 6.0	27.0 ± 1.5	MYO 1100 mg + DCI 27.6 mg + FA 400 µg 1/day MYO 2g + FA 200 µg 2/day	125	27.9 ± 4.9	26.7 ± 1.6	FA 200 µg 2/day

BMI: body mass index; d: day; DCI: 1D-*chiro*-inositol; FA: folic acid; MYO: myoinositol; SD: standard deviations.

2013; Dell'Edera et al., 2017).

The incidence of GD, as diagnosed by an OGTT between 24 and 28 GW, which was the main judgement criterion, was reported in all nine studies selected for the meta-analysis. To study the secondary judgement criteria, only eight were selected.

The rate of CS was reported in six of the studies (Celentano et al.,

2020; D'Anna et al., 2012; D'Anna et al., 2015; D'Anna et al., 2013; Santamaria et al., 2016; Farren et al., 2017), that of macrosomia also in six (D'Anna et al., 2012; D'Anna et al., 2015; D'Anna et al., 2013; Santamaria et al., 2016; Farren et al., 2017; Dell'Edera et al., 2017), that of prematurity in seven studies (Celentano et al., 2020; D'Anna et al., 2012; D'Anna et al., 2015; D'Anna et al., 2013; Santamaria et al., 2016; Farren

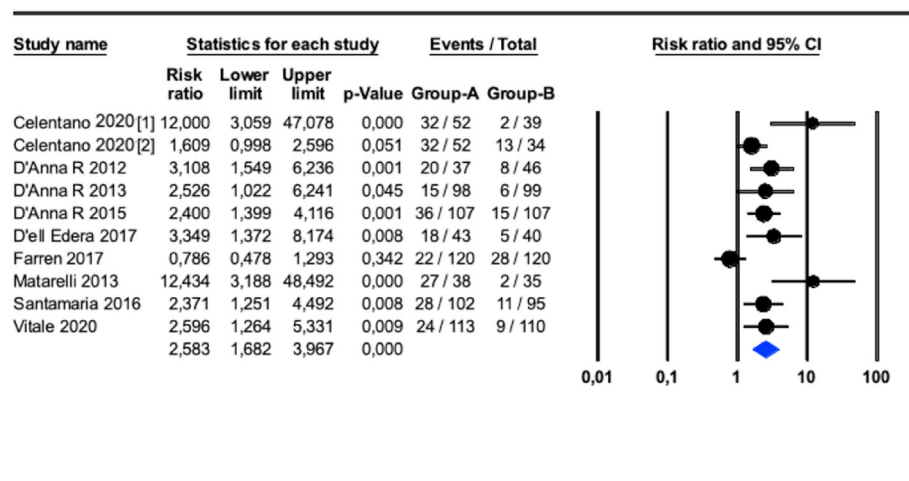


Fig. 2. Forest Plot for the meta-analysis on the incidence of gestational diabetes

$I^2 = 72\%$, $p < 0.001$.

GRADE MODERATE: the authors believe that the true effect is probably close to the estimated effect.

Group A: placebo group; Group B: myo-inositol group.

$I^2 = 72\%$, $p < 0.001$.

GRADE MODERATE: the authors believe that the true effect is probably close to the estimated effect.

Group A: placebo group; Group B: myo-inositol group.

et al., 2017; Dell'Edera et al., 2017) and that of neonatal hypoglycemia again in seven (D'Anna et al., 2015; D'Anna et al., 2013; Matarrelli et al., 2013; Santamaria et al., 2016; Farren et al., 2017; Dell'Edera et al., 2017). Gestational hypertension or pre-eclampsia was observed in four studies (D'Anna et al., 2012; D'Anna et al., 2015; D'Anna et al., 2013; Santamaria et al., 2016). Finally, the proportion of patients whose management required initiation of insulin therapy was documented in six studies (Celentano et al., 2020; D'Anna et al., 2012; D'Anna et al., 2015; D'Anna et al., 2013; Matarrelli et al., 2013; Santamaria et al., 2016).

• Main judgement criterion: the incidence of gestational diabetes

Data from the nine studies included in the meta-analysis suggest that the risk of GD occurring was significantly greater in the placebo group than in patients receiving myoinositol supplementation (RR = 2.58, CI 95% [1.68; 3.97], $p < 0.001$) with wide variability between the studies ($I^2 = 71.94\%$, $p < 0.001$) and high potential publication bias (Egger's test: $p = 0.001$) (Figs. 2 and 3). The results of the studies of Farren et al. (2017), of Matarrelli et al. (2013) and of group 1 in the study performed by Celentano et al. (2020) were the furthest removed from those of the other studies and probably contributed to the extent of heterogeneity. A sensitivity analysis was performed after exclusion of these studies and the results suggest that the incidence of GD was still significantly higher in patients receiving placebo (RR = 2.31, CI 95% [1.81; 2.96], $p < 0.001$) (Figs. 4 and 5). The extent of heterogeneity was satisfactory ($I^2 = 0\%$, $p = 0.70$) with an improvement of potential bias publication ($p = 0.04$). The incidence of GD was also analysed by stratification of the doses of myoinositol used in the different selected publications. The results are shown in Fig. 6. A daily dose of 4g of myoinositol was the most widely used regimen in the studies, which all showed that the risk of GD was significantly greater in the placebo groups (RR = 3.16, CI 95% [2.15; 4.62], $p < 0.001$) with only slight variations from one publication to another ($I^2 = 37.55$, $p = 0.14$). In contrast, no significant result was observed for the combination of 1100 mg of myoinositol and 27.6 mg of 1D-*chiro*-inositol described in two of the studies (Celentano et al., 2020; Farren et al., 2017).

• Secondary judgement criteria

In comparison with the groups receiving placebo, there was no notable effect in the pregnant patients of myoinositol supplementation on the rates of CS (RR = 1.16, CI 95% [0.96; 1.41], $p = 0.13$, Egger's test: $p < 0.001$; and after sensitivity analysis: RR = 1.14 CI 95% [0.98; 1.32], $p = 0.09$; Egger's test: $p = 0.31$), neonatal hypoglycemia (RR = 2.51, CI

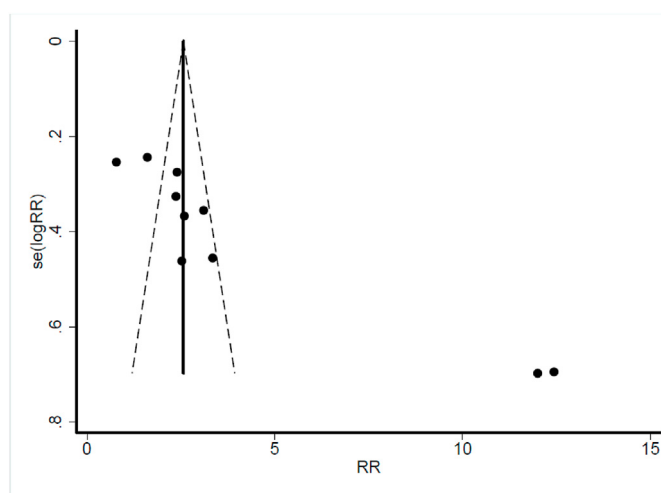


Fig. 3. Funnel Plot for the meta-analysis on the incidence of gestational diabetes.

95% [0.57; 11.15], $p = 0.23$; Egger's test: $p = 0.47$), macrosomia (RR = 1.65, CI 95% [0.62; 4.39], $p = 0.32$; Egger's test: $p = 0.11$), and gestational hypertension and pre-eclampsia (RR = 1.74, CI 95% [0.60; 5.04], $p = 0.31$; Egger's test: $p = 0.07$). Likewise, myoinositol supplementation had no significant effect on the number of patients requiring insulin therapy for management of their GD (RR = 2.08, CI 95% [0.83; 5.24], $p = 0.12$; Egger's test: $p = 0.33$). In contrast, the rates of prematurity were significantly higher in patients on placebo than in those administered myoinositol supplements (RR = 2.15, CI 95% [1.32; 3.49], $p = 0.002$; Egger's test: $p = 0.47$) (Figs. 7 and 8).

4. Discussion

• Discussion of the main results

Nine studies were included in the meta-analysis involving a total of 1546 participants. Of these patients, 801 received the intervention (myoinositol alone or myoinositol + 1D-*chiro*-inositol), which had no documented adverse effects. Myoinositol supplementation was associated with a significant reduction in the incidence of GD ($p < 0.001$) and also had a significant effect on the rate of prematurity ($p = 0.02$). In contrast, there was no difference between the groups in the rates of Cesarean section, neonatal hypoglycemia, macrosomia, gestational hypertension, pre-eclampsia, and insulin therapy.

Stratified subgroup analysis of the type of intervention (myoinositol 2000 mg twice a day vs myoinositol 1100 mg + 1D-*chiro*-inositol 27.6 mg/day vs myoinositol 1750 mg + 1D-*chiro*-inositol 250 mg + zinc 12.5 mg + methylsulfonylmethane 10 mg/day) showed a significant improvement in terms of GD in patients who had received supplements at a dose of 2000 mg twice a day. In contrast, daily administration of myoinositol at a dose of 1100 mg in combination with 27.6 mg of 1D-*chiro*-inositol had no beneficial effect. The combination of 1750 mg of myoinositol and 250 mg of 1D-*chiro*-inositol with 12.5 mg of zinc and 10 mg of methylsulfonylmethane was studied in only one of the trials included in the meta-analysis and hence no conclusions can be drawn on any possible benefit of the treatment. In addition, this combination of several molecules makes it difficult to interpret the specific effect of myoinositol in the intervention.

The results of this analysis suggest, therefore, that the combination of myoinositol and 1D-*chiro*-inositol, which is also an isomer of inositol, is of no benefit in the prevention of GD.

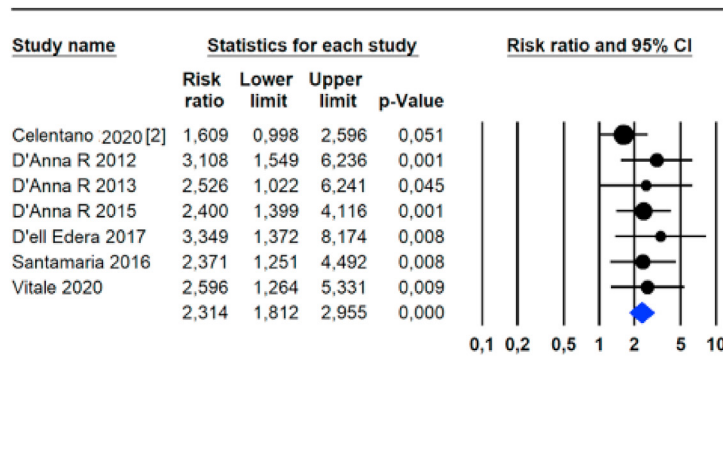
In their trial published in 2020, Celentano et al. (2020) also studied the effect of supplementation with 1D-*chiro*-inositol at a dose of 500 mg/day in combination solely with FA. The intervention had no positive impact on the incidence of GD compared to treatment with FA alone administered to another group, which is consistent with our previous results. A meta-analysis published in 2019 (Zhang et al., 2019) of the relation between myoinositol supplementation and the incidence of GD included five randomized controlled trials involving 927 pregnant women. The results also showed a significant decrease in the incidence of GD in patients receiving myoinositol supplements. They are in agreement with those of our meta-analysis, which analysed a larger number of patients because it included more recently published trials.

• Limitations of the study

This meta-analysis has certain potential limitations that need to be addressed.

First, all the studies were carried out in Europe (8 in Italy and 1 in Ireland), where the population is mainly Caucasian, which restricts the possibility of extending the results to other ethnic groups.

Second, there was significant heterogeneity in the sensitivity analyses. One possible explanation is the differences between the administration of the myoinositol supplements: the doses used ranged from 1100 mg to 4000 mg, and in three of the studies myoinositol was given in combination with 1D-*chiro*-inositol, another isomer of inositol, thereby



$I^2 < 0.001$, $p = 0.704$.

GRADE HIGH: the authors have a lot of confidence that the true effect is similar to the estimated effect.

Fig. 4. Forest Plot for the sensitivity analysis on the primary endpoint (incidence of gestational diabetes)

$I^2 < 0.001$, $p = 0.704$.

GRADE HIGH: the authors have a lot of confidence that the true effect is similar to the estimated effect.

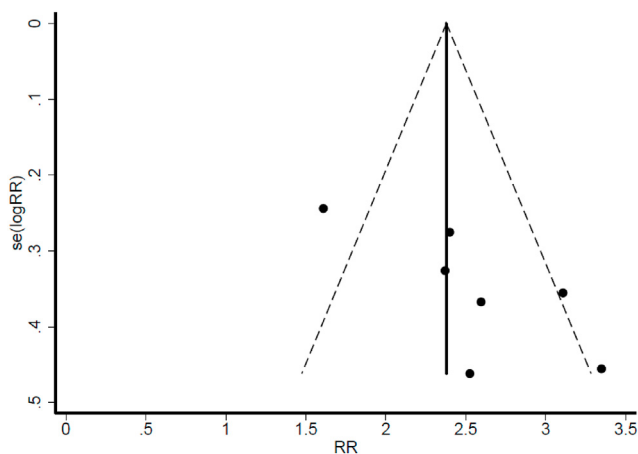


Fig. 5. Funnel Plot for the sensitivity analysis on the primary endpoint (incidence of gestational diabetes).

affecting comparability between the studies.

Third, although all the studies involved patients identified as being at risk of developing GD, the selected risk factors (and therefore the inclusion criteria) varied between the studies (OGTT, family history of type 2 diabetes, overweight or obesity) and thus the mechanisms underlying the disease also differed. Hence, although the findings show a strong relation between myoinositol supplementation and a decrease in the incidence of GD, further clinical trials are needed to clarify the advantages and disadvantages of supplementation on the basis of individual profiles.

Fourth, the findings of our meta-analysis could also be limited by the methodological flaws of the trials analysed. The nature of the intervention did not allow for blinding of the personnel or the patients and thus entailed a high risk of performance bias. In addition, one of the trials included was a retrospective case-control study and so of a lower quality than a randomized controlled trial.

Finally, the studies had relatively small sample sizes (including one trial $n < 100$), and were mostly monocentric with a low number of events concerning the secondary judgement criteria, factors that may have limited the control quality of the preuvers.

Multicentre trials with bigger patient populations are therefore needed to better assess the impact of myoinositol supplementation on the risks during GD of maternal (gestational hypertension, pre-eclampsia, CS) and fetal (macrosomia, prematurity, neonatal hypoglycemia) complications.

• Implications

The incidence of GD has greatly risen over the last 20 years along with the worldwide trend of older maternal age at pregnancy and an increase in the number of obese women of childbearing age.

GD is associated with numerous obstetrical complications that are fetal or neonatal as well as maternal and so its rising incidence must be considered as a major public health problem. As there is a lack of reliable and effective approaches for the prevention of GD, identifying new targeted therapeutic strategies is of prime importance.

Inositol isomers are a group of molecules that play a role in regulation of numerous hormonal and metabolic pathways in the human body. They are present in different natural food groups such as cereals, legumes and fruits and are therefore absorbed daily. Taken in the form of oral supplements, these isomers are unlikely to be a risk for the health of mother or fetus. Myoinositol is one of the most common stereoisomers of inositol and acts as an insulin sensitizing agent. Various metabolic disorders such as type 2 diabetes and PCOS have been associated with an imbalance in the myoinositol to 1D-*chiro*-inositol ratio (Heimark et al., 2014). Studies of women with PCOS or type 2 diabetes have shown a significant improvement in insulin resistance following administration of these inositol isomers (Pintaudi et al., 2016). The metabolic changes are accompanied by the return of regular menstrual cycles and an increased chance of conception in women with oligomenorrhea (Pundir et al., 2018).

Myoinositol supplementation initiated at the beginning of pregnancy could thus be a new prevention strategy for GD. It is safe to administer to patients, could be easier to implement than strategies based solely on dietary measures or regular physical activity and for these reasons would probably achieve better compliance. In particular, the administration of 2000 mg of myoinositol twice a day could reduce the incidence of GD in at-risk patients.

Most of the evidence available for our analysis was of relatively low quality, and further randomized controlled trials of better quality, with

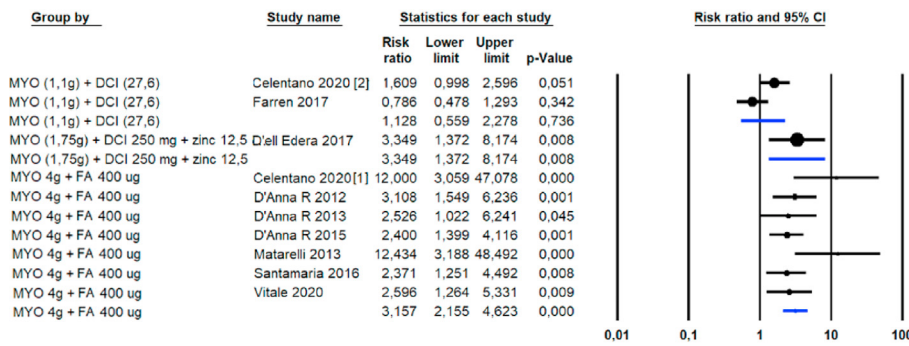


Fig. 6. Forest Plot of the analysis after stratification on the posology
 $I^2 = 76\%$, $p = 0.042$ (2 studies)
 I^2 not estimated (1 study)
 $I^2 = 38\%$, $p = 0.142$ (7 studies)
 GRADE LOW: the true effect might be markedly different from the estimated effect.

$I^2=76\%$, $p=0.042$ (2 studies)

I^2 not estimated (1 study)

$I^2=38\%$, $p=0.142$ (7 studies)

GRADE LOW: the true effect might be markedly different from the estimated effect.

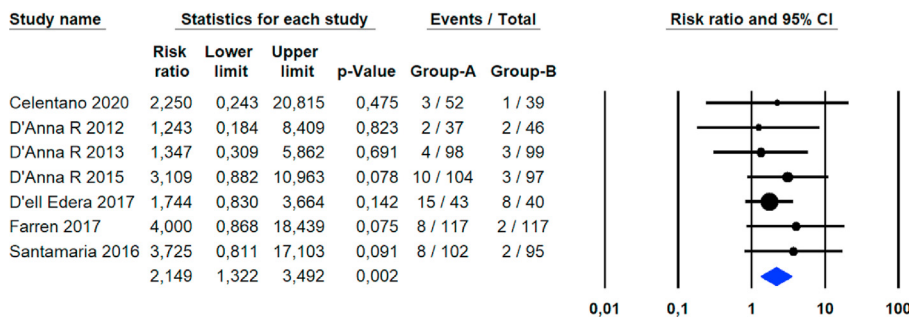


Fig. 7. Forest Plot for meta-analysis on prematurity rate
 $I^2 < 0.001$, $p = 0.871$.
 GRADE HIGH: the authors have a lot of confidence that the true effect is similar to the estimated effect.
 Group A: placebo group; Group B: myoinositol group.

$I^2 < 0.001$, $p = 0.871$.

GRADE HIGH: the authors have a lot of confidence that the true effect is similar to the estimated effect.

Group A: placebo group; Group B: myoinositol group.

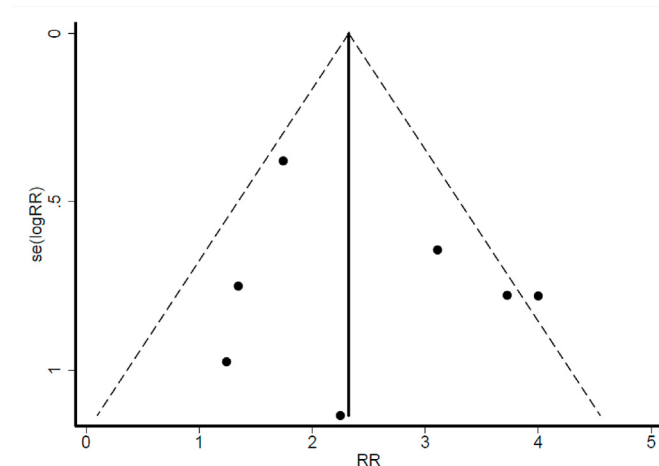


Fig. 8. Funnel Plot for meta-analysis on prematurity rate.

bigger sample sizes, and a greater representation of ethnic groups would be necessary to confirm the efficacy and optimal dose of myoinositol in the prevention of GD.

Statements and declarations

No update of a previous systematic review.
 No commercial or financial conflict, no funding sources for all authors.
 No sponsor

CRedit authorship contribution statement

Anthéa Bertrand: Conceptualization, Data curation, Methodology.
Denis Gallot: Supervision. **Bruno Pereira:** Formal analysis. **Amélie Delabaere:** Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

- Baillargeon, J.P., Nestler, J.E., Ostlund, R.E., Apridonidze, T., Diamanti-Kandarakis, E., 2008. Greek hyperinsulinemic women, with or without polycystic ovary syndrome, display altered inositols metabolism. *Hum. Reprod. Oxf. Engl.* juin 23 (6), 1439–1446.
- Carlomagno, G., Unfer, V., 2011. Inositol safety: clinical evidences. *Eur. Rev. Med. Pharmacol. Sci.* août 15 (8), 931–936.
- Celentano, C., Matarrelli, B., Pavone, G., Vitacolonna, E., Mattei, P.A., Berghella, V., et al., 2020. The influence of different inositol stereoisomers supplementation in pregnancy on maternal gestational diabetes mellitus and fetal outcomes in high-risk patients: a randomized controlled trial. *J. Matern.-Fetal. Neonatal. Med. Off. J. Eur. Assoc. Perinat Med Fed Asia Ocean Perinat. Soc. Int. Soc. Perinat. Obstet. mars* 33 (5), 743–751.
- Corrado, F., D'Anna, R., Di Vieste, G., Giordano, D., Pintaudi, B., Santamaria, A., et al., 2011. The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes. *Diabet. Med. J. Br. Diabet. Assoc.* août 28 (8), 972–975.
- Croze, M.L., Soulage, C.O., 2013. Potential role and therapeutic interests of myo-inositol in metabolic diseases. *Biochimie.* oct 95 (10), 1811–1827.
- Dell'Edera, D., Sarlo, F., Allegretti, A., Simone, F., Lupo, M.G., Epifania, A.A., 2017. The influence of D-chiro-inositol and D-myo-inositol in pregnant women with glucose intolerance. *Biomed. Rep.* août 7 (2), 169–172.
- DerSimonian, R., Laird, N., 2015. Meta-analysis in clinical trials revisited. *Contemp Clin. Trials.* nov 45 (Pt A), 139–145.
- D'Anna, R., Di Benedetto, V., Rizzo, P., Raffone, E., Interdonato, M.L., Corrado, F., et al., 2012. Myo-inositol may prevent gestational diabetes in PCOS women. *Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol.* juin 28 (6), 440–442.
- D'Anna, R., Scilipoti, A., Giordano, D., Caruso, C., Cannata, M.L., Interdonato, M.L., et al., 2013. myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. *Diabetes Care.* avr 36 (4), 854–857.
- D'Anna, R., Di Benedetto, A., Scilipoti, A., Santamaria, A., Interdonato, M.L., Petrella, E., et al., 2015. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. *Obstet. Gynecol.* août 126 (2), 310–315.
- Facchinetti, F., Pignatti, L., Interdonato, M.L., Neri, I., Bellei, G., D'Anna, R., 2013. 60: myoinositol supplementation in pregnancies at risk for gestational diabetes. Interim analysis of a randomized controlled trial (RCT). *Am. J. Obstet. Gynecol.* 1 janv 208 (1, Suppl. ment), S36.
- Farren, M., Daly, N., McKeating, A., Kinsley, B., Turner, M.J., Daly, S., 2017. The prevention of gestational diabetes mellitus with antenatal oral inositol supplementation: a randomized controlled trial. *Diabetes Care.* juin 40 (6), 759–763.
- Faticelli, F., Celentano, C., Zecca, I.A., Di Vieste, G., Pintaudi, B., Liberati, M., et al., 2018. Effect of inositol stereoisomers at different dosages in gestational diabetes: an open-label, parallel, randomized controlled trial. *Acta Diabetol.* août 55 (8), 805–812.
- Griffith, R.J., Alswelker, J., Moore, A.E., Brown, S., Middleton, P., Shepherd, E., et al., 2020. Interventions to prevent women from developing gestational diabetes mellitus: an overview of Cochrane Reviews. *Cochrane Database Syst. Rev.* 11 juin 6, CD012394.
- Heimark, D., McAllister, J., Lerner, J., 2014. Decreased myo-inositol to chiro-inositol (M/C) ratios and increased M/C epimerase activity in PCOS theca cells demonstrate increased insulin sensitivity compared to controls. *Endocr. J.* 61 (2), 111–117.
- Higgins, J.P.T., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses, 6 sept *BMJ* 327 (7414), 557–560.
- Higgins, J.P.T., Altman, D.G., Gøtzsche, P.C., Jüni, P., Moher, D., Oxman, A.D., et al., 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, 18 oct *BMJ* 343, d5928.
- Lerner, J., 2002. D-chiro-inositol—its functional role in insulin action and its deficit in insulin resistance. *Int. J. Exp. Diabetes Res.* 3 (1), 47–60.
- Malvasi, A., Kosmas, I., Mynbaev, O.A., Sparic, R., Gustapane, S., Guido, M., et al., 2017. Can trans resveratrol plus d-chiro-inositol and myo-inositol improve maternal metabolic profile in overweight pregnant patients? *Clin. Ter.* août 168 (4), e240-7.
- Matarrelli, B., Vitacolonna, E., D'Angelo, M., Pavone, G., Mattei, P.A., Liberati, M., et al., 2013. Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: a randomized controlled trial. *J. Matern.-Fetal. Neonatal. Med. Off. J. Eur. Assoc. Perinat. Med. Fed. Asia Ocean Perinat Soc Int Soc. Perinat Obstet.* juill 26 (10), 967–972.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., PRISMA Group, 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg Lond Engl* 8 (5), 336–341.
- Pintaudi, B., Di Vieste, G., Bonomo, M., 2016. The effectiveness of myo-inositol and D-chiro inositol treatment in type 2 diabetes. *Internet J. Endocrinol.*, 9132052, 2016.
- Pundir, J., Psaroudakis, D., Savnur, P., Bhide, P., Sabatini, L., Teede, H., et al., 2018. Inositol treatment of anovulation in women with polycystic ovary syndrome: a meta-analysis of randomised trials. *BJOG Int. J. Obstet. Gynaecol.* févr 125 (3), 299–308.
- Santamaria, A., Di Benedetto, A., Petrella, E., Pintaudi, B., Corrado, F., D'Anna, R., et al., 2016. Myo-inositol may prevent gestational diabetes onset in overweight women: a randomized, controlled trial. *J. Matern.-Fetal Neonatal. Med. Off. J. Eur. Assoc. Perinat. Med. Fed Asia Ocean Perinat. Soc. Int. Soc. Perinat. Obstet.* oct 29 (19), 3234–3237.
- Vitale, S.G., Corrado, F., Caruso, S., Di Benedetto, A., Giunta, L., Cianci, A., et al., 2021. Myo-inositol supplementation to prevent gestational diabetes in overweight non-obese women: bioelectrical impedance analysis, metabolic aspects, obstetric and neonatal outcomes - a randomized and open-label, placebo-controlled clinical trial. *Int. J. Food Sci. Nutr.* août 72 (5), 670–679.
- Wojciechowska, A., Osowski, A., Józwick, M., Górecki, R., Rynkiewicz, A., Wojtkiewicz, J., 2019. Inositols' importance in the improvement of the endocrine-metabolic profile in PCOS. *Int. J. Mol. Sci.* 18 nov 20 (22), E5787.
- Zhang, H., Lv, Y., Li, Z., Sun, L., Guo, W., 2019. The efficacy of myo-inositol supplementation to prevent gestational diabetes onset: a meta-analysis of randomized controlled trials. *J. Matern.-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet.* juill 32 (13), 2249–2255.