OBSTETRICS

Clinical and metabolic outcomes in pregnant women at risk for gestational diabetes mellitus supplemented with myo-inositol: a secondary analysis from 3 RCTs

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BACKGROUND: Gestational diabetes mellitus is defined as carbohydrate intolerance that begins or is first recognized during pregnancy. Insulin sensitizing substances such as myo-inositol have been considered for the prevention of gestational diabetes mellitus and related complications.

OBJECTIVE: Because previous studies failed to show a clear reduction of gestational diabetes mellitus complications, the aim of this study was to evaluate clinical and metabolic outcomes in women who are at risk for gestational diabetes mellitus supplemented with myo-inositol since the first trimester.

STUDY DESIGN: A secondary analysis of databases from 3 randomized, controlled trials (595 women enrolled) in which women who were at risk for gestational diabetes mellitus (a parent with type 2 diabetes mellitus, obese, or overweight) were supplemented with myo-inositol (4 g/d) throughout pregnancy. Main measures were the rate of adverse clinical outcomes: macrosomia (birthweight, ≥4000 g), large-for-gestational-age babies (fetal growth, ≥90 percentile), fetal growth restriction (fetal growth, ≤3 percentile), preterm birth (delivery before week 37 since the last menstruation), gestational hypertension, and gestational diabetes mellitus.

RESULTS: A significant reduction was observed for preterm birth (10/291 [3.4%] vs 23/304 [7.6%]; $P=.03$), macrosomia (6/291 [2.1%] vs 16/304 [5.3%]; $P=.04$), Large-for-gestational-age babies (14/291 [4.8%] vs 27/304 [8.9%]; $P=.04$) with only a trend to significance for gestational hypertension (4/291 [1.4%] vs 12/304 [3.9%]; $P=.07$). Gestational diabetes mellitus diagnosis was also decreased when compared with the control group (32/291 [11.0%] vs 77/304 [25.3%]; $P<.001$). At univariate logistic regression analysis, myo-inositol treatment reduced the risk for preterm birth (odds ratio, 0.44; 95% confidence interval, 0.20–0.93), macrosomia (odds ratio, 0.38; 95% confidence interval, 0.14–0.98), and gestational diabetes mellitus diagnosis (odds ratio, 0.36; 95% confidence interval, 0.23–0.57).

CONCLUSION: Myo-inositol treatment in early pregnancy is associated with a reduction in the rate of gestational diabetes mellitus and in the risk of preterm birth and macrosomia in women who are at risk for gestational diabetes mellitus.

Key words: gestational diabetes mellitus, insulin resistance, myo-inositol, outcome

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that begins or is first recognized during pregnancy.[1] GDM affects fetal (preterm birth, macrosomia, stillbirth), neonatal (trauma for shoulder dystocia, hypoglycemia, transfer to an intensive care unit), and maternal health (hypertensive disorders, operative deliveries).[2] The Hyperglycemia and Adverse Pregnancy Outcomes study[3] allowed the International Association of the Diabetes and Pregnancy Study Groups to publish up-graded recommendations for the diagnosis and classification of hyperglycemia during pregnancy.[4] Our group adhered to such recommendations and almost doubled the number of GDM diagnoses. Although diet and insulin are established treatments, we believe that the management of GDM should include prevention measures. According to the last Cochrane reviews, lifestyles changes that include diet and physical activity stimulation provided inconsistent results; GDM was affected only in a subpopulation of women.[5] Conversely, an individual patient data metaanalysis recently has shown that diet and physical activity may reduce the GDM rate significantly.[6] The American College of Obstetricians and Gynecologists recommends insulin as first-line therapy when target glucose levels cannot be achieved and considers metformin only a reasonable second-line approach to treat GDM.[7] Conversely, the Society of Maternal-Fetal Medicine proposed metformin as a reasonable and safe first-line pharmacologic alternative to insulin because of a lower cost and a higher patient compliance rate.[8] Also, glyburide has been proposed as a first-line therapy for GDM treatment, but it has not still approved by US Food and Drug Administration for this indication.[9] On the other hand, insulin-sensitizing substances, namely metformin and myo-inositol (MI) have also been considered for the prevention of GDM and related complications. Contrasting results have been reported with the use of metformin[10,11] and MI seems promising[12,13] although some concerns need to be addressed.[14] MI is a polyol (Figure), 1 of the 9 stereoisomeric forms of inositol, which is linked to phospholipids in the membranes of all living cells. It is produced endogenously from D-glucose; substantial amounts are present in foods such as cantaloupe, melons, and citrus fruits and in vegetables, beans, and peas. MI is considered a second messenger of insulin action,[15] which may increase insulin

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AJOG at a Glance

Why was this study conducted?

Three previous randomized controlled trials have demonstrated that myo-inositol may reduce the gestational diabetes mellitus rate in pregnancies that are at risk; they failed to show changes in gestational diabetes mellitus–related complications.

Key Findings

Myo-inositol that is given daily at a dosage of 4 g throughout pregnancy reduces the rate of macrosomia and preterm birth compared with only folic acid treatment.

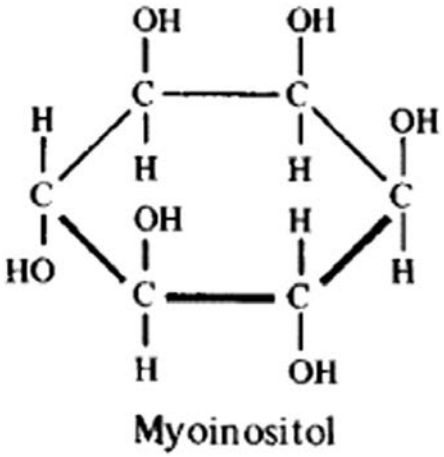
What does this add to what is known?

In addition to gestational diabetes mellitus, myo-inositol supplementation early in pregnancy may prevent preterm birth and macrosomia in women who are at risk for gestational diabetes mellitus.

sensitivity and provide more available phosphatidylinositol, which has an important role in the relation of insulin with its receptor.[16] That is the reason that it was first used in hyperinsulinemic infertile women who were affected by polycystic ovary syndrome, with the aim to restore ovarian cycle and fertility.[17] Afterwards, MI was used successfully in other conditions that were characterized by increased insulin resistance, such as metabolic syndrome[18] and GDM.[19] In a small retrospective study, women with polycystic ovary syndrome were supplemented with MI throughout pregnancy, which allowed a relevant reduction in GDM diagnosis.[20] Then, our group performed 3 randomized, controlled trials that supplemented MI for the prevention of GDM in women with different risk factors.[21–23]

The aim of this study was to evaluate clinical and metabolic outcomes for which previous trials lacked statistical power. Because the trials were performed almost in parallel, a pooled analysis was not planned previously.

FIGURE
Myo-inositol formula



An isomeric form of Inositol.

H, hydrogen; *HO*, hydroxyl group; *OH*, hydroxyl.

Santamaria et al. GDM complication rate in women supplemented with myo-inositol. Am J Obstet Gynecol 2018.

Methods

The study built an unique database from the 3 randomized, controlled trials, in which MI was supplemented at the end of the first trimester (12–13 weeks of gestation) to delivery at a dose of 2 g plus 200 μg of folic acid vs 200 μg of folic acid (placebo group) twice each day. Each 1 of the previous studies included women with different risk factors for GDM, namely a parent affected by type 2 diabetes mellitus, obesity (body mass index, ≥30 kg/m^2), or overweight (body mass index, ≥25 to <30 kg/m^2); both body mass indexes were evaluated on prepregnancy values.

All the studies were open-label, and the randomization was computerized, with an allocation of 1:1 in each group. Inclusion criteria, in each study, depended on the population of women at risk of GDM. In all the studies, the primary outcome was the GDM rate. Instead, in this secondary analysis, there were several primary outcomes that included rate of gestational hypertension, preterm birth, macrosomia, large-for-gestational-age (LGA) babies and fetal growth restriction. At 24–28 weeks of gestation, women underwent a 75-g 2-hour oral glucose tolerance test (OGTT). Threshold values were ≥92 mg/dL fasting, ≥180 mg/dL at 1 hour after load, and ≥153 mg/dL at 2 hours after load. One of the 3 values that exceeds or equals the threshold was diagnostic of GDM. *Gestational hypertension* was defined as blood pressure ≥140/90 mm Hg that was measured twice, at least 6 hours apart, after 20 weeks of gestation (with or without proteinuria); *macrosomia* was considered at a birthweight of ≥4000 g; LGA babies and fetal growth restriction were evaluated according to Italian Charts on neonatal anthropometric measures, as ≥ 90th percentile and ≤ 3rd percentile, respectively;[24] *preterm birth* was defined as delivery at <37 weeks gestation or 259 days since the last menstrual period. Homeostatic model assessment (HOMA) index was calculated in the following manner: fasting glucose (milligram/deciliter)× fasting insulin (milli-international units/liter)/405. Outcome measures were obtained by the specific database of the women who were involved in the 3 trials. Women who met GDM criteria received a specific diet and/or insulin when required, according to glucose values.

The numeric data are expressed as mean±standard deviation, and the categoric variables are expressed as count and percentage. The Kolmogorov-Smirnov test, Mann-Whitney test, and chi-square test were applied where appropriate. The univariate logistic regression model was estimated on the whole sample to highlight the outcomes that were influenced by MI treatment. Results of univariate analysis are reported as probability value, odds ratio (OR), and 95% confidence interval (CI). A multivariate analysis was performed to assess ORs for treatment with MI and recognized risk factors for GDM, such as prepregnancy body mass index, ethnicity, parity, maternal age, family history of diabetes mellitus, HOMA

value at first trimester, and weight gain at OGTT. Statistical analysis was performed with IBM SPSS Statistics for Windows (version 22; IBM Corporation, Armonk, NY). A probability value of $<.05$ was considered statistically significant.

Results

Of 660 women who were enrolled in the 3 previous trials, data were analyzed in those who complete the study, which allowed 291 women to be assigned randomly to MI and 304 women to be assigned to placebo (Table 1). Overall, there were 7 midtrimester miscarriages; 34 women abandoned the studies before the OGTT for various reasons, and 24 women delivered in other hospitals for whom it was impossible to collect the outcomes. Their baseline features are reported in Table 2; no differences were found between the MI and placebo groups. Of the 65 drop-outs, 40 were before the OGTT; thus, the outcomes were not valuable for an intention-to-treat analysis, and 25 were after the OGTT. However, we performed an intention-to-treat analysis, which did not show results different from those of "per protocol analysis." Moreover, we evaluated the clinical characteristics of the women who abandoned the trial, but no significant differences from those who concluded the trial were found. The outcomes of OGTT showed a significantly lower prevalence of GDM in MI (11%) than in the placebo group (25.3%; OR, 0.36; 95% CI, 0.23−0.57). Similarly, highly significant differences were found for each of the glucose values that were measured at OGTT (Table 3). All the women who experienced GDM in both group were treated by diet; only 2 women in the MI obese group and 9 women in the placebo group needed insulin.

Mean gestational age at delivery and birthweight were similar in both groups; a reduction of preterm birth ($P=.03$), macrosomia ($P=.04$), and LGA babies ($P=.04$) was found in women who received MI compared with the placebo group (Table 4). A difference that was not significant was observed for the rate of gestational hypertension, even if it was reduced > 60%. There was no difference in the rate of fetal growth restriction between groups. In Table 5, data concerning only patients with GDM of either group are reported. There was a significant statistical difference in the HOMA index (2.97 vs 2.30) at baseline, in birthweight ($P=.01$), in the 1-hour glucose value ($P=.004$), and in maternal weight gain at OGTT ($P=.02$) between groups.

When we performed univariate logistic regression analysis, it was possible to appreciate how MI treatment may influence metabolic and clinic outcomes (Table 6). In particular, MI treatment significantly reduced GDM onset by 66% (OR, 0.34; $P<.001$) and improved fasting (OR, 0.37; $P=.001$) and the 2-hour glucose values (OR, 0.44; $P=.01$). Similarly, a decreased risk in the MI group was obtained for preterm birth (OR, 0.44; $P=.03$) and macrosomia (OR, 0.38; $P=.04$), with border line values for LGA (OR, 0.52; $P=.05$) and gestational hypertension (OR, 0.34; $P=.06$). A multivariate logistic regression analysis was performed, with preterm birth, macrosomia and gestational hypertension as dependent variables, MI supplementation as an independent variable, and the other risk factor for GDM as covariates. This model showed that both MI supplementation and HOMA value at first trimester independently affected the preterm rate ($P=.04$; 95% CI, 0.21−0.97; $P=.02$; 95% CI, 1.02−1.28, respectively). For macrosomia and gestational hypertension, a borderline significance related to MI treatment was evidenced ($P=.05$; 95% CI, 0.15−1.03; $P=.06$; 95% CI, 0.10−1.08, respectively). The compliance to the supplement was assessed during the period of hospitalization

TABLE 1
First outcome measure for the pregnant women who concluded all 3 trials

Risk factor	Myo-inositol, n	Placebo, n	Gestational diabetes mellitus rate, %
Parent with type 2 diabetes mellitus	99	98	6 vs 15.3
Obesity	97	104	14 vs 33.6
Overweight	95	102	11.6 vs 27.4
TOTAL	291	304	

Santamaria et al. GDM complication rate in women supplemented with myo-inositol. Am J Obstet Gynecol 2018.

TABLE 2
General characteristics of both groups at baseline

Characteristic	Myo-inositol (n=291)	Placebo (n=304)	*P* value
Maternal age, y[a]	31.3±5.4	32.0±5.4	.09
Prepregnancy body mass index, kg/m^2[a]	27.9±5.4	28.3±5.1	.27
Nulliparous, %	50.2	48.7	.72
Homeostatic model assessment−insulin resistance[a]	2.2±2.0	2.2±2.1	.51
A parent with type 2 diabetes mellitus, n (%)	99 (34.0)	98 (32.2)	.64
Not caucasian, n (%)	31 (10.6)	37 (12.2)	.73
Women with previous preterm birth, n (%)	9 (3.1)	8 (2.6)	.93

[a] Data are given as mean±standard deviation.

Santamaria et al. GDM complication rate in women supplemented with myo-inositol. Am J Obstet Gynecol 2018.

TABLE 3
Clinical and metabolic outcomes at oral glucose tolerance test (24–28 weeks gestation) in both groups

Outcome	Myo-inositol (n=291)	Placebo (n=304)	*P* value
Gestational age, d[a]	181.7±9.6	182.0±10.9	.70
Increased weight at oral glucose tolerance test, kg[a]	6.4±3.6	6.4±4.1	.80
Glucose value, mg/dL[a]			
At baseline	79.3±7.9	82.7±9.3	<.001
After 1 hr	126.6±31.6	136.4±31.6	<.001
After 2 hr	105.8±24.6	115.4±28.5	<.001
Gestational diabetes mellitus diagnosis, n (%)	32 (11.0)	77 (25.3)	<.001

[a] Data are given as mean±standard deviation.

Santamaria et al. GDM complication rate in women supplemented with myo-inositol. Am J Obstet Gynecol 2018.

with a short questionnaire. No one dropped out for the adverse effects attributable to the supplement. In fact, no one abandoned the study for these reasons.

Comment

This study was a secondary analysis of 3 randomized, controlled trials, in which MI was administered at the same dose and for the same period throughout pregnancy to women with different risk factors for GDM (ie, family history,[21] obesity,[22] or overweight[23]). Although confirming a significant reduction of GDM rate in women who received MI in comparison with placebo, we also demonstrated a reduction of preterm birth rate and in the rates of macrosomia and LGA babies. Indeed, MI supplementation reduced the risk for macrosomia and preterm birth by 60% and 50%, respectively, as shown by univariate and multivariate analysis. Although fewer women in the MI arm still experienced GDM. Interestingly, they show a worse metabolic profile (higher HOMA) than counterparts who experienced GDM in the placebo arm. This suggests that failures of MI in the prevention of GDM are related to personal characteristics.

It is important to note that MI is a nutritional supplement, and, consequently, it has a good compliance in pregnant women. In addition, as also confirmed by this study, MI has a good tolerability[25] and does not appear to be harmful for the fetus.[16]

This study has some weakness. Because of limited sample size, it is still underpowered for some low-prevalence outcomes in the Italian population, as for the case of hypertensive disorders. Furthermore, data for total gestational weight gain was not available.

Another limitation is the design of primary trials, none of them were performed in a double-blind way. Moreover, the secondary analysis that we reported was merged outcomes in a retrospective process.

A possible strength of the study was the pooled analysis that included individual patients rather than aggregate data. Moreover, the primary trials were homogeneous, performed in the same population and with similar methods. Another group recently performed a small randomized, controlled study and reported a protective effect of MI in pregnant women with elevated first-trimester serum glucose levels (≥100 mg/dL).[26] All these positive findings were not confirmed in a very recent placebo controlled study in which a 70% lower amount of MI (1200 mg/d) plus 27.6 mg/d of D-chiro-inositol was given in women who were at risk because of a family history of type 2 diabetes mellitus.[27] A possible explanation of this failure might be the dose of MI, which suggests a dose-related mechanism of the supplement.

Other insulin sensitizers, such as metformin, have been tested previously for the prevention of GDM and related complications. In women with polycystic ovary (a population at risk because of insulin resistance), a metaanalysis demonstrated that metformin treatment was associated with the same rate of GDM as placebo.[10] Moreover, a recent RCT performed in obese class II and class III women (another population affected by insulin resistance because of excessive fat tissue) also demonstrated the inefficacy of metformin in the prevention of both GDM and LGA babies.[28] The reason that MI and metformin behave differently is unknown.

TABLE 4
Clinical outcomes in both groups

Outcome	Myo-inositol (n=291)	Placebo (n=304)	*P* value
Gestational age at delivery, wk[a]	38.8±1.6	38.9±1.7	.38
Fetal weight, g[a]	3188±468	3246±523	.14
Preterm birth, n (%)	10 (3.4)	23 (7.6)	.03
Macrosomia (≥4 kg), n (%)	6 (2.1)	16 (5.3)	.04
Large for gestational age (≥90th percentile), n (%)	14 (4.8)	27 (8.9)	.04
Gestational hypertension, n (%)	4 (1.4)	12 (3.9)	.07
Fetal growth restriction (≤3rd percentile), n (%)	4 (1.4)	3 (1.0)	.70

[a] Data are given as mean±standard deviation.

Santamaria et al. GDM complication rate in women supplemented with myo-inositol. Am J Obstet Gynecol 2018.

TABLE 5
Comparison between pregnant women with gestational diabetes mellitus in the myo-inositol and placebo group

Variable	Myo-inositol (n=32)[a]	Placebo (n=77)[a]	*P* value
Maternal age, y	32.6±5.5	32.5±5.1	.63
Body mass index, kg/m^2	28.6±4.5	30.2±5.1	.32
Homeostatic model assessment (1st trimester)	2.97±1.7	2.30±2.2	.01
Gestational age at oral glucose tolerance test, d	180.5±6.9	181.1±13.7	.59
Glucose value, mg/dL			
Baseline	89.9±7.2	92.5±9.6	.30
After 1 hr	181.8±33.4	165.6±29.4	.004
After 2 hr	140.8±29.3	141.5±29.4	.95
Increased weight at oral glucose tolerance test, kg	7.2±4.1	5.5±4.3	.02
Gestational age at delivery, d	265.8±9.8	270.9±13.7	.002
Fetal weight, g	3003±627	3281±592	.01

[a] Data are given as mean±standard deviation.

Santamaria et al. GDM complication rate in women supplemented with myo-inositol. Am J Obstet Gynecol 2018.

A possible explanation could be found in their mechanisms of action. MI increases insulin sensitivity through both the enhancement of insulin transduction signal and the reduction of fat (and free fatty acid) deposition.[29] Metformin has demonstrated to decrease in hepatic glucose production, mostly through a mild and transient inhibition of the mitochondrial respiratory-chain complex 1.[30]

In conclusion, starting early in pregnancy, MI supplementation reduced preterm birth and large infants, in addition to preventing GDM development in approximately two-thirds of the population. Further larger and double-blind studies are needed to confirm MI efficacy on mother-infant health. ■

TABLE 6
Univariate logistic regression analysis on myo-inositol treatment

Outcome	P value	Odds ratio	95% Confidence interval
Gestational diabetes mellitus	<.001	0.36	0.23–0.57
Gestational hypertension	.06	.34	0.11–1.06
Preterm birth	.03	.44	0.20–0.93
Macrosomia	.04	.38	0.14–0.98
Large for gestational age	.05	.52	0.27–1.01
Fetal growth restriction	.66	1.39	0.31–6.30
Glucose value			
At baseline	.001	.37	0.20–0.66
After 1 hr	.26	.72	0.41–1.27
After 2 hr	.01	.44	0.23–0.86

Santamaria et al. GDM complication rate in women supplemented with myo-inositol. Am J Obstet Gynecol 2018.

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