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.

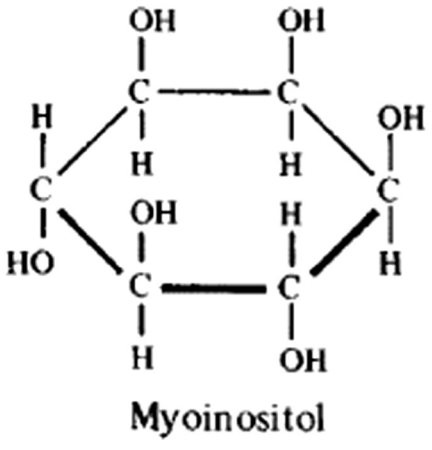
What does this add to what is known?

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.

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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