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Myo-Inositol for the Prevention of Gestational Diabetes Mellitus. A Brief Review

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Summary Gestational Diabetes Mellitus (GDM) is one of the most frequent complications of pregnancy and is characterized by a carbohydrate intolerance which is diagnosed with the oral glucose tolerance test. The prevalence of GDM in our population is about 12%, but risk factors like a previous GDM, ethnicity, a parent with diabetes mellitus type 2 and maternal overweight may increase its occurrence. Complications of GDM are a pre-term birth (before 37 wk gestation), macrosomia (birth weight ≥4 kg) and gestational hypertension. Actually, GDM is principally treated with diet and, if it is necessary, with insulin; but the challenge is the prevention of GDM. Among the measures used, changes in life-style (diet+exercise) failed to prevent GDM whereas metformin showed conflicting results. A promising supplement is myo-inositol (MI) which was given from first trimester until delivery to women at risk for GDM reporting a significant decrease in GDM occurrence by more than 60% comparing to the placebo group. Recently, a secondary analysis from 3 randomized controlled trials demonstrated that MI may also significantly reduce some of GDM complications such as pre-term birth and macrosomia with a favorable impact on mother and fetus well being.
Key Words gestational diabetes mellitus, insulin resistance, macrosomia, myo-inositol

Introduction

Gestational Diabetes Mellitus (GDM) is defined as "carbohydrate intolerance of varying degree of severity with onset or first recognition during pregnancy" (*1*). According to the majority of the clinical guidelines for the management of diabetes in pregnancy, the screening and diagnosis of GDM should be undertaken between the 24th and 28th wk of pregnancy. After a fasting evaluation of plasma glucose, the oral glucose tolerance test (OGTT) is performed with 75 g of glucose and then glucose level is measured after 1 and 2 h. At least one of the three glucose values over or equal to the cut-off (fasting 92 mg/dL, after 1 h 180 mg/dL and after 2 h 153 mg/dL) was enough for diagnosis of GDM. There are some recognizable risk factors for GDM such as maternal age >35 y old, previous GDM, ethnicity, family history of diabetes mellitus type 2 and maternal overweight. Once diagnosed, GDM is treated with diet, but in about 20% of cases addition of insulin is needed. Major complications of GDM are macrosomia (fetal weight ≥4 kg), pre-term birth (delivery <37th week gestation) and gestational hypertension. Each of them may significantly worsen pregnancy outcome; thus, the challenge is to prevent GDM and its complications. From a review of the literature, the actual strategies for preventing GDM are three: 1) changes in lifestyle (diet + exercise); 2) metformin and 3) myo-inositol. A recent meta-analysis by Cochrane Database (*2*) on 23 trials that had involved 6,633 women, randomized to diet and exercise vs no intervention failed to demonstrate a significant difference between the 2 groups (p=0.07; RR 0.85; CI 0.71–1.01). Conflicting results were obtained with metformin, given from the beginning of pregnancy principally to women affected by polycystic ovary syndrome (PCOS). In a recent meta-analysis by Zeng XL et al. (*3*), a significant reduction of GDM rate was observed in retrospective studies, but not in randomized controlled trials.

The protocol of the 3 studies was consistent with the principles of the Declaration of Helsinki, and all participants gave their written informed consent. The trial was approved by the ethical committee of Messina University Hospital (E347/2008).

Role of Myo-Inositol

Inositol is a polyol existing in nine isomeric forms; myo-inositol (MI) is the most abundant one. We can find it in our food, but is also sufficiently produced by the human body from D-glucose. Larner J et al. (*4*) demonstrated that MI may be converted to another isomer D-chiro-inositol (DCI) by an epimerase; both are contained in inositol phoshoglycans (IPGs), which act as insulin mediators. In particular, at the end of a complicated process, glucose trans membrane transporters (GLUT 4) are activated by IPGs allowing glucose entrance into the cells. This insulin like mechanism of IPGs may reduce insulin production and consequently its plasma levels with beneficial effects on endocrine and

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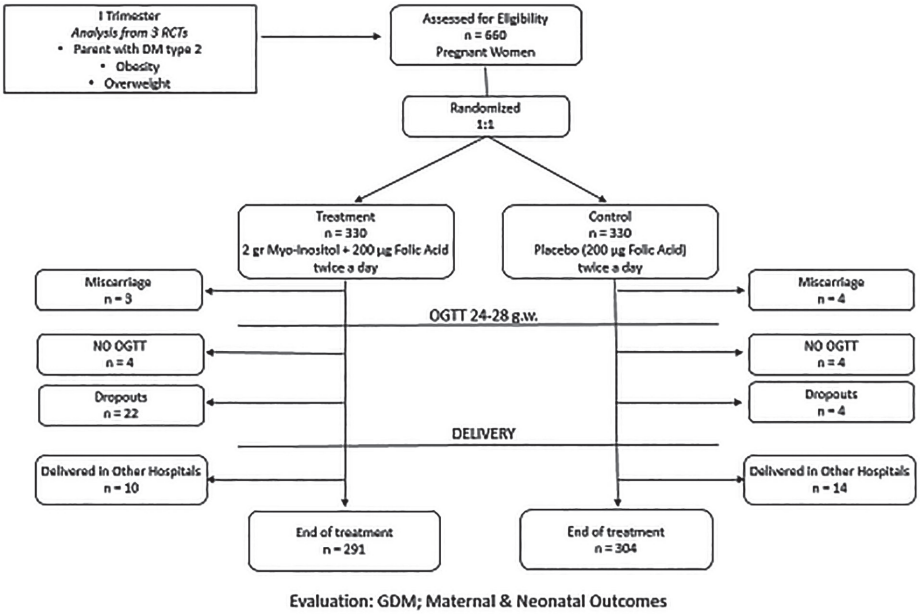

Fig. 1. Flowchart of the study.

metabolic disorders such as PCOS (5). Later on, some Italian groups demonstrated that giving MI to infertile women with PCOS could restore spontaneous ovarian activity and consequently fertility. Those surprising results were obtained through a decrease of insulin levels confirming the role of inositol as second messenger of insulin. In our first study, we considered retrospectively 98 hyperinsulinemic infertile women with PCOS that became pregnant after a treatment with MI or metformin (6). In the group treated with metformin, it was stopped after a positive pregnant test and it was considered a control group whereas in the other group MI was given until delivery. All the women underwent an OGTT thus we could evaluate whether MI treatment might prevent GDM in such cohort of high risk women. The difference between groups in GDM rate was highly significant (17.4% vs control, $p<0.001$) suggesting, for the first time, that MI may prevent GDM occurrence in women with PCOS. Afterwards, our group began 3 randomized, controlled studies, recruiting in each trial a different kind of women at risk for GDM: 1) a parent with type 2 diabetes mellitus (7), obese (8), overweight (9). In all these studies, MI was given at a dosage of 2 g twice a day from the end of first trimester until delivery. Primary outcome was the reduction of GDM rate in the treated group, and surprisingly it was more than 60% in the MI group with similar statistically significant decrease in all the trials; in particular, 6% vs 15.3% in the study with a parent affected by type 2 diabetes mellitus; 14% vs 33.6% with obese women and 11.6% vs 27.4% with overweight women. Instead, for secondary outcomes, which were the clinical outcomes such as macrosomia (fetal birth weight ≥4 kg), pre-term birth (delivery at <37th week gestation) and gestational hypertension, the differences were not so much significant as for the GDM rate. Then, with the aim to asses a possible decrease of GDM complications too, we performed a secondary analysis putting together the databases of the 3 previous studies and considering a total of 660 women enrolled (10) as reported in Fig. 1. This last study confirmed the significant decrease of GDM rate (Table 1), but also a significant decrease in macrosomia, large for gestational age fetus (>90 percentile) and preterm birth rate in the group treated with MI (Table 1). Univariate logistic regression analysis assessed that the significant decrease in GDM rate , macrosomia and preterm birth depends on MI treatment. Furthermore, a recent meta-analysis (11) confirmed our results on MI effect in decreasing the risk of GDM rate and pre-term birth. In conclusion, our studies have demonstrated that MI supplementation, given from first trimester to delivery in women at risk may reduce not only GDM rate but also its principal complications.

Table 1. Relevant results.

Outcomes	Myo-inositol (n=291)	Placebo (n=304)	p value
GDM n (%)	32 (11.0)	77 (25.3)	<0.001
LGA (≥90° percentile) n (%)	14 (4.8)	27 (8.9)	0.04
Macrosomia (≥4 kg) n (%)	6 (2.1)	16 (5.3)	0.04
Preterm birth n (%)	10 (3.4)	23 (7.6)	0.03

GDM, Gestational Diabetes Mellitus; LGA, Large for gestational age fetus.

Disclosure of State of COI

No conflicts of interest to be declared.

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