Myo-inositol supplementation for the treatment of gestational diabetes mellitus - Minireview and a new protocol

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Gestational diabetes (GDM) is defined as a glucose intolerance resulting in hyperglycaemia of variable severity with onset during pregnancy. Placental hormones are the principal responsible of increased insulin resistance through the pregnancy, aiming to support fetal growth. Consequently, at 34-36 weeks of a non-complicated pregnancy, insulin sensitivity value may less than half compared to pre-pregnancy levels [1]. Consequently, GDM is a lack of pancreatic β-cells function occurring when this is unable to face insulin demand through the pregnancy. Some women are at major risk to develop GDM, depending on obesity, previous GDM, ethnic group, a parent with type diabetes, etc. Following the recommendations for the diagnosis and classification of hyperglycaemia during pregnancy suggested by the "International Association of Diabetes in Pregnancy Study Group" (IADPSG) [2], and in accordance with the Italian Guidelines [3], an Oral Glucose Tolerance Test (OGTT) is offered to all the women with recognizable risk factors for GDM. However, our group demonstrated that among women without risk factors, there was a 23% that developed GDM [4]. When GDM is diagnosed, first measures are lifestyle changes with diet plus physical activity for 2 weeks. When target glucose levels cannot be achieved, insulin is the first line therapy in Italy because oral therapy, such as metformin, is out of label. However, it's well-known that insulin may cause side effects such hypoglycaemia, weight gain and an increase in hypertensive disorders [5]. In the last years, myo-inositol, the most abundant isomer of inositol in nature, has been used during pregnancy either to prevent GDM [6-8] or to treating it [9,10]. Myo-inositol is a polyol, which is linked to phospholipids in the cell membranes. Great amounts of myo-inositol are found in fresh fruits and vegetables, but also in meat; human cells may synthesize myo-inositol by themselves and the kidneys are the most important regulator of myo-inositol metabolism. In the tissues expressing a specific enzyme epimerase, the conversion of myo-inositol to the other isomer D-chiro-inositol can occur [11]. Myo-inositol and D-chiro-inositol are involved as components of glycosyl-phosphatidylinositol (GPI) and of inositol phosphoglycans (IPGs), considered second messengers of insulin action in the GPI/IPG pathway [12]. Kennington AS et al. [13] demonstrated that in human subjects affected by diabetes mellitus type 2, which is similar in its pathogenesis to GDM, an imbalance between myo-inositol and D-chiro-inositol occurs, with a decreased urinary excretion of D-chiro-inositol and an increased urinary excretion of myo-inositol. Depletion of intracellular myo-inositol may also depend on inhibition of myo-inositol uptake due a competition with glucose, which is particularly abundant in diabetic patients and structurally similar to myo-inositol, saturating myo-inositol transporters [14]. Depletion of intracellular myo-inositol consequently decreases the production of D-chiro-inositol reducing the availability for their incorporation into IPGs, putative second messengers of insulin. This hypothesis was confirmed by an experimental study which demonstrated a decreased IPG level in muscle biopsies in type 2 diabetic patients, contributing to insulin resistance in the target tissues [13]. All these considerations induced the authors of a recent review on myo-inositol to suggest a therapeutic use of myo-inositol and/or D-chiro-inositol supplementation in diabetes mellitus to restore depleted tissue levels of these 2 inositols [15]. First study on myo-inositol supplementation in women affected by GDM was carried out about 10 years ago by our group [16]. In this randomized, controlled study, 92 women with GDM diagnosed from 24 to 28 weeks gestation were involved, 28 received, after diet recommendations, myo-inositol plus folic acid (2 g plus 200 µg twice/day) and 56 only folic acid 200 µg twice a day for 8 weeks. Primary outcomes were the variation of insulin resistance (calculated with Homeostasis Model Assessment, HOMA) and of adiponectin plasma value, which is a marker of insulin sensitivity. After 8 weeks of treatment, a significant difference in insulin resistance and adiponectin concentrations between groups was shown. In another study by Lubin et al. [10], regarding a small group of women with GDM not controlled by diet, myo-inositol was used as first-line of treatment in alternative to insulin, reporting only a 25% of failure, in which cases insulin administration was necessary. However, Authors claimed that the reduction of insulin use was statistically significant compared to the control group. In a prospective, randomized, controlled study also D-chiro-inositol has been used in 137 women with GDM at a dosage of 500 mg twice a day [17]. The Authors found significantly lower median weight gain, lower number of insulin injections, lower median abdominal circumference in the newborns, but not lower birth weight in the group of women treated with D-chiro-inositol. A study of comparison among different combinations of inositols supplement was published last year [18]. In this study, 80 women with Polycystic Ovary Syndrome (PCOS) were enrolled divided in 4 arms, with different dosages of myo-inositol and D-chiro-inositol and 1 of placebo. A significant lower birth weight in all the treated groups compared to placebo group was shown, but only in the myo-inositol group a decreased insulin resistance and reduced weight gain and

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insulin treatment compared to the control group was highlighted. Despite the encouraging results reported in several studies, an impaired myo-inositol oral absorption may result in a reduced clinical effect [19]; thus, a strategy to overcome this problem is to enhance the absorption rate of myo-inositol with better therapeutic effects. A recent study has demonstrated that myo-inositol absorption when orally administered with α-lactalbumin is improved in non-responder patients [20]. A possible explanation of this effect, suggested by in vitro findings, maybe the behavior of the peptides deriving from α-lactalbumin digestion, which may modulate tight junction permeability allowing increased absorption of myo-inositol [20]. Furthermore, a recent clinical study [21] has confirmed this experimental data. In this study, 37 anovulatory women affected by PCOS were treated for 3 months with myo-inositol (4 g/die) obtaining an ovulation in 24 cases. The remaining resistant women were treated with myo-inositol (4 g/die) plus α-lactalbumin (150 mg/die) obtaining, after 3 months, an ovulation with increased plasma myo-inositol concentration [21].

New protocol: myo-inositol plus α-lactalbumin for the treatment of gestational diabetes mellitus ClinicalTrials.gov Identifier: NCT03763669

Design
The study is a randomized, prospective, placebo-controlled trial, including the first 80 consecutive gestational diabetes patients diagnosed, according to the Italian Guidelines, from November 2018 to December 2019, in the Department of Obstetrics and Gynecology of Messina University (ITALY). After an informed written consent, participants will be randomly assigned to receive (n. 40) diet and folic acid (4 g/die) obtaining an ovulation in 24 cases. The remaining resistant women were treated with myo-inositol (4 g/die) plus α-lactalbumin (150 mg/die) obtaining, after 3 months, an ovulation with increased plasma myo-inositol concentration [21].

Outcome measures
Primary outcomes: Insulin resistance changes measured with HOMA-IR and abdominal circumference centile variations from baseline to the end of treatment
Secondary outcomes: 1) birth weight, 2) obstetrical complications: macrosomia (> 4 kg), pre-term birth, gestational hypertension
Expected results: A significant decrease in insulin resistance and abdominal circumference through the study period in the treated group compared to the placebo group.

Conflicts of interest
None

References

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