SPANDIDOS PUBLICATIONS

BIOMEDICAL REPORTS 7: 169-172, 2017

The influence of D-*chiro*-inositol and D-*myo*-inositol in pregnant women with glucose intolerance

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Received April 24, 2017; Accepted May 23, 2017

DOI: 10.3892/br.2017.939

Abstract. The aim of the present study was to demonstrate that the use of inositol and folic acid from the first trimester of pregnancy, counteracts the onset of gestational diabetes mellitus (GDM) in women at risk, preserving the infants from macrosomia, hypoglycemia and preterm delivery. The authors collected data from the pregnant women at the laboratory (Unit of Cytogenic and Molecular Genetics), from January 2014 to April 2016, all with first trimester fasting plasma glucose (FPG) >92 mg/dl. A total of 40 women were treated with 250 mg/day D-*chiro*-inositol, 1.75 g/day D-*myo*-inositol, 12.5 mg/day zinc, 10 mg/day methylsulfonylmethane, 400 μg/day 5-methyltetrahydrofolic acid. The other 43 women (control group) were treated with only 400 μg/day folic acid. The primary outcome measure was the incidence of maternal GDM. The secondary outcome measures were the incidence of fetal macrosomia, preterm delivery and neonatal hypoglycemia. At the 24th week of pregnancy, the incidence of maternal GDM was recorded in 18 women in the control group and in 5 women in the treated group [relative risk (RR)=3.35; 95% confidence interval (CI)=1.37-8.17; P=0.0028). A significant difference was observed between treated and control groups in terms of risk of macrosomia. A total of seven infants in the control group, and two in the treated group, weighed >4,000 g (RR=5,12; 95% CI=1.21-21.68; P=0.0099). No significant difference was identified between two groups, regarding the other two secondary outcomes, neonatal hypoglycemia (RR=4.650; 95% CI=0.57-38.11; P=0.1086) and preterm delivery (RR=1.74; 95% CI=0.83-3.66; P=0.1301). The current study demonstrated the potential benefit of supplementation with the association of D-*chiro*-inositol and D-*myo*-inositol in pregnant 'at risk' women, with first trimester FPG >92 mg/dl, in preventing the onset of maternal GDM and macrosomia in newborns.

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Abbreviations: FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; HbA1c, glycosylated hemoglobin

Key words: D-*chiro*-inositol, D-*myo*-inositol, folic acid, fasting blood glucose, gestational diabetes mellitus

Introduction

Gestational diabetes mellitus (GDM) is defined as 'carbohydrate intolerance of variable severity with onset or first recognition during pregnancy' (1). It usually subsides following pregnancy, but also significantly increases a woman's risk of both type 2 diabetes and cardiovascular disease in the postpartum period.

Pregnancy, due to placental hormone action, is characterized by a physiological increase of insulin resistance (IR), which has the aim to promote the use of nutrients by the fetus, especially in the second and third trimesters of pregnancy (2), however, this physiological mechanism could lead to the onset of GDM (3).

The diagnosis of GDM is usually made using an oral glucose tolerance test between 24-28 weeks' gestation and is associated to risks for the fetus, including macrosomia (birth weight >4,000 g) and birth injuries such as shoulder dystocia, or problems in newborns such as neonatal hypoglycemia, respiratory distress syndrome, childhood obesity, and for the mother, such as caesarean delivery, hypertensive disorders and an increased risk of developing type 2 diabetes later in life (4).

Both pharmacological (oral antidiabetic drugs or insulin) and non-pharmacological (dietary and lifestyle counseling) interventions are used to treat GDM, with the aim to control hyperglycemia.

Historically, insulin has been the therapeutic agent of choice for controlling hyperglycemia in pregnant women. However, difficulty in medication administration with multiple daily injections, potential for hypoglycemia and increase in appetite and weight make this therapeutic option cumbersome for many pregnant patients, often presenting suboptimal compliance (5).

Moreover, hypoglycemia occurs in ~71% of women who take insulin at some time during their pregnancy (5). The use of oral hypoglycemic drugs has become an attractive option in pregnancy; among these, the authors focused metformin.

Metformin acts by decreasing hepatic glucose output by inhibition of gluconeogenesis and enhances peripheral glucose uptake in the muscles and adipose tissues. It also decreases intestinal glucose absorption, reduces both fasting and postprandial plasma glucose and increases insulin sensitivity (5).

Oral hypoglycemics and/or insulin therapy are recommended for women with GDM who are unable to maintain glycemic control with dietary and lifestyle interventions alone (6).

However, the use of hypoglycemic drugs has reported adverse effects as the potential risks of neonatal hypoglycemia and teratogenicity associated with placental transfer to the fetus (7,8).

There is a need for safe, simple and efficacious interventions to prevent the development of GDM. In order to prevent perinatal complications of mothers and infants mentioned above, the goal of glycemic control during pregnancy should be to bring plasma glucose level as close to normal as possible without development of hypoglycemia (9).

Inositol (1,2,3,4,5,6-hexahydroxycyclohexane) is a cyclitol naturally present in animal and plant cells, either in its free form or as a bound-component of phospholipids or inositol derivatives.

It exists under nine stereoisomeric forms and *myo*-inositol is the predominant isomeric form, it is broadly distributed in eukaryotic tissues and cells in which acts as second messenger, regulating the activities of several hormones such as follicle stimulating hormone, thyroid stimulating hormone and insulin (10).

Whereas the intracellular inositol pool is >99% constituted by *myo*-inositol in most tissues, significant differences have been recorded in the concentration of *myo*-inositol and D-*chiro*-inositol, another important stereoisomer, in fat, muscle and liver (10). This different distribution reflects the distinct functions that likely the two isomers are playing in those tissues, and their respective proportions are actively maintained as *myo*-inositol is enzymatically transformed into D-*chiro*-inositol through a NAD, NADH-dependent epimerase, according to tissue requirement, the enzymatic reaction stimulated by insulin (10).

Abnormalities in *myo*-inositol and in D-*chiro*-inositol metabolism have been involved in the development of several diseases and in particular in the development of IR and diabetic complications (11,12).

The objective of the present study was to demonstrate that, in the preconceptional period, D-*chiro*-inositol and D-*myo*-inositol first of all prevent the onset of GDM in women at risk, and protect infants from macrosomia, preterm delivery and hypoglycemia.

Materials and methods

Patient data. From January 2014 to April 2016, the authors collected data derived from 93 women in pregnancy arrived in the laboratory (Laboratory of Cytogenetic and Molecular Genetics) for the first trimester screening for aneuploidy by using nuchal translucency sonography and analysis of proteins and placental hormones (bi-test or combined test). A statement of informed consent was signed by all women according to principles of Helsinki Declaration. These women had a fasting plasma glucose value in the first trimester >92 mg/dl.

Table I. Baseline parameters of both groups.

Parameter	Treated group (n=40)	Control group (n=43)	P-value
Age (years)	32.50±3.56	32.34±3.78	ns
BMI (kg/m^2)	25.62±4.03	26.86±3.12	ns
SBP (mmHg)	118.50±12.02	119.56±10.20	ns
DBP (mmHg)	68.46±8.78	67.32±8.52	ns
FBG (mg/dl)	85.78±7.13	85.20±7.35	ns
HbA1c (mmol/mol)	31.85±8.25	31.55±7.80	ns
Hb (g/dl)	13.10±1.52	12.87±1.67	ns

Data are presented as mean ± standard deviation. P<0.05 was considered to indicate a statistically significant difference. Ns, no significant; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; Hb, hemoglobin.

A total of 40 women were treated with 250 mg/day of D-*chiro*-inositol, 1.75 g/day D-*myo*-inositol, 12.5 mg/day zinc, 10 mg/day methylsulfonylmethane and 400 mg/day 5-methyl-tetrahydrofolic acid. The other 43 women (control group) were treated with only 400 mg/day of folic acid.

The primary outcome measure was the incidence of maternal GDM. The secondary outcome measures were the requirement of maternal insulin therapy, the incidence of fetal macrosomia and neonatal hypoglycemia.

The inclusion criteria were as follows: Preconceptional (1 month before conception) supplementation with folic acid, no previous diabetes mellitus, Caucasian women with singleton pregnancy without GDM, whose first degree relative was not affected by type-2 diabetes and hypertension; whose BMI <30 kg/m^2; an elevated fasting glucose (glycemia ≥5.1 mmol/l or 92 mg/dl and ≤7.0 mmol/l or 126 mg/dl) according to IADPSG Guidelines (13) and hypocaloric and low-glycemic index diet according to standard care.

The exclusion criteria were as following: BMI ≥30 kg/m^2, previous GDM, pre-gestational diabetes, first trimester glycosuria, first degree relative affected by type 2 diabetes or hypertension, fasting plasma glucose <126 mg/dl or random glycaemia <200 mg/dl, hemoglobin (Hb) <10 g/dl, carrier of thalassemic trait, sickle cell anemia, twin pregnancy, therapy with corticoids, not caucasian or with polycystic ovary syndrome.

Statistical analysis. Statistical analysis was carried out with SPSS software (version, 17; SPSS, Inc., Chicago, IL, USA). Data are expressed as means ± standard deviation for categorical variables. The means of independent groups were compared using Student's t test after checking for normal distribution. For analysis of paired data, Student's t-test was also used.

The relative risk (RR) with 95% confidence intervals (CIs) was calculated for non-parametric parameters. P<0.05 was considered to indicate a statistically significant difference.

Table II. Incidence of primary and secondary outcomes in treated and control groups following the 24th week of pregnancy.

Outcome	Treated group (n=40)	Control group (n=43)	RR (95% CI)	P-value
Primary outcome				
Onset of GDM	5	18	3.35 (1.37-8.17)	0.0028
Secondary outcome				
Macrosomia (>4 kg)	2	11	5.12 (1.21-21.68)	0.0099
Neonatal hypoglycemia	1	5	4.65 (0.57-38.11)	0.1086
Preterm delivery	8	15	1.74 (0.83-3.66)	0.1301

RR, relative risk; CI, confidence interval. P<0.05 was considered to indicate a statistically significant difference.

Results

The study involved data from 92 women, however were excluded: Seven women due to Hb value <10 g/dl and two due to midtrimester miscarriage. Therefore, the authors collected data from 40 women treated with inositol and folic acid (treated group) and from 43 women with supplementation only with folic acid (control group).

No statistical difference was identified, at baseline, between two groups, in terms of age, BMI, systolic and diastolic blood pressure, FBG, HbA1c and Hb values (Table I).

Following the 24th week of pregnancy, the incidence of maternal GDM was recorded in 18 women in the control group and in 5 women in the treated group (RR=3.35; 95% CI=1.37-8.17; P=0.0028) (Table II). A significant difference was observed between treated and control groups for the risk of macrosomia; seven infants, in the control group, weighed >4 kg and two in the treated group (RR=5.12; 95% CI=1.21-21.68; P=0,0099) (Table II).

No significant difference was observed between two groups, regarding the other two secondary outcomes, neonatal hypoglycemia (RR=4.650; 95% CI=0.57-38.11; P=0.1086) and preterm delivery (RR=1.74; 95% CI=0.83-3.66; P=0,1301).

Discussion

To date, the treatment options currently available to women with GDM are restricted to subcutaneous insulin therapy however, it may present side effects such as hypoglycemia, increased weight gain during pregnancy, which are themselves linked to adverse pregnancy outcomes, and it requires self-injection (14). Metformin is an effective treatment for GDM and other disorders of IR, but often requires additional treatment with insulin in order to maintain adequate glycemic control (14). Furthermore, it is also known to cross the placenta, and the long-term effects on the unborn child are still unknown (15).

For these reasons, much research is dedicated to the development of alternative treatments (14).

Due to its role as a second messenger in the signal transduction processes, several clinical trials (10-16) have suggested a beneficial effect of inositol (*myo-* or *chiro-*) supplementation in improving ovarian function, hormone status and glucose homeostasis, with no reported side effects, For this reason, it may potentially be used on a population-wide level.

Moreover, Corrado *et al* (17) demonstrated a greater decrease in markers for IR among gestational diabetic women with dietary supplementation randomly exposed to *myo*-inositol plus folic acid as compared with folic acid alone.

The current results matched with those obtained by D'Anna *et al* (12), in their study highlighting a reduction in terms of incidence of GDM and fetal macrosomia, in women with only family history of type 2 diabetes treated with 4 g *myo*-inositol + 400 mg/day compared to the placebo group, who were only treated with folic acid 400 mg/day.

Moreover, according to Matarrelli *et al* (18), the finding that maternal/fetal/neonatal GDM in women at high risk, was well controlled in the *myo*-inositol group, was confirmed.

Therefore, the present study demonstrates that the supplementation with D-*chiro*-inositol and D-*myo*-inositol gives good control of maternal glycemia and good perinatal outcomes, and further studies are needed to compare these with those offered by the treatment with insulin or oral hypoglycemic drugs.

Despite the limited number of study population, the authors proposed that, in order to prevent the onset of GDM, the dosage of 250 mg/day D-*chiro*-inositol and of 200 mg/day D-*myo*-inositol may be an optimal dosage in pregnant women at risk for GDM, with first trimester FBG >92 mg/dl, and could represent a possible alternative to oral antidiabetic drugs, when their use is not possible (for example in metformin intolerance or drug contraindications).

However, further studies are required to explore the optimal dose of inositol supplementation, and to establish long-term safety, involving a larger number of patients from different ethnicities and with different risk factors for GDM.

In order to prevent perinatal complication of mothers and infants, and to avoid risk of adverse outcomes in pregnancy and in the long term, there is a urgent need to reinforce preconceptional care. The current study demonstrates the potential benefit of supplementation with the association of D-*chiro*-inositol and D-*myo*-inositol in pregnant 'at risk' women, with first trimester FBG of >92 mg/dl, in preventing the onset of maternal GDM and macrosomia in newborns.

Acknowledgements

The authors would like to thank 'Associazione Gian Franco Lupo-Un Sorriso Alla Vita' (ONLUS: non-profit organization of social utility).

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