The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: 1476-7058 (Print) 1476-4954 (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf20

The influence of different inositol stereoisomers supplementation in pregnancy on maternal gestational diabetes mellitus and fetal outcomes in high-risk patients: a randomized controlled trial

Claudio Celentano, Barbara Matarrelli, Giulia Pavone, Ester Vitacolonna, Peter A. Mattei, Vincenzo Berghella & Marco Liberati

To cite this article: Claudio Celentano, Barbara Matarrelli, Giulia Pavone, Ester Vitacolonna, Peter A. Mattei, Vincenzo Berghella & Marco Liberati (2018): The influence of different inositol stereoisomers supplementation in pregnancy on maternal gestational diabetes mellitus and fetal outcomes in high-risk patients: a randomized controlled trial, The Journal of Maternal-Fetal & Neonatal Medicine, DOI: 10.1080/14767058.2018.1500545

To link to this article: https://doi.org/10.1080/14767058.2018.1500545

Published online: 17 Dec 2018.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
https://doi.org/10.1080/14767058.2018.1500545

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

The influence of different inositol stereoisomers supplementation in pregnancy on maternal gestational diabetes mellitus and fetal outcomes in high-risk patients: a randomized controlled trial

Claudio Celentano[a], Barbara Matarrelli[a], Giulia Pavone[a], Ester Vitacolonna[b], Peter A. Mattei[c], Vincenzo Berghella[d] and Marco Liberati[a]

[a]Department of Obstetrics and Gynaecology, University of Chieti, Chieti, Italy; [b]Department of Medicine and Science of Aging, University of Chieti, Chieti, Italy; [c]ITAB Institute of Advanced Biomedical Technologies, University of Chieti, Chieti, Italy; [d]Department of Obstetrics and Gynecology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

ABSTRACT

Objective: To identify the effects of different dietary inositol stereoisomers on insulin resistance and the development of gestational diabetes mellitus (GDM) in women at high risk for this disorder.

Design: A preliminary, prospective, randomized, placebo controlled clinical trial.

Participants: Nonobese singleton pregnant women with an elevated fasting glucose in the first or early second trimester were studied throughout pregnancy.

Intervention: Supplementation with myo-inositol, D-chiro-inositol, combined myo- and D-chiro-inositol or placebo.

Main outcome measure: Development of GDM on a 75 grams oral glucose tolerance test at 24–28 weeks' gestation. Secondary outcome measures were increase in BMI, need for maternal insulin therapy, macrosomia, polyhydramnios, neonatal birthweight and hypoglycemia.

Results: The group of women allocated to receive myo-inositol alone had a lower incidence of abnormal oral glucose tolerance test (OGTT). Nine women in the control group (C), one of the myo-inositol (MI), five in D-chiro-inositol (DCI), three in the myo-inositol/D-chiro-inositol group (MI/DCI) required insulin ($p = .134$). Basal, 1-hour, and 2 hours glycemic controls were significantly lower in exposed groups ($p < .001$, .011, and .037, respectively). The relative risk reduction related to primary outcome was 0.083, 0.559, and 0.621 for MI, DCI, and MI/DCI groups.

Conclusions: This study compared the different inositol stereoisomers in pregnancy to prevent GDM. Noninferiority analysis demonstrated the largest benefit in the myo-inositol group. The relevance of our findings is mainly related to the possibility of an effective approach in GDM. Our study confirmed the efficacy of inositol supplementation in pregnant women at risk for GDM.

ARTICLE HISTORY
Received 12 May 2018
Revised 11 July 2018
Accepted 11 July 2018

KEYWORDS
D-chiro-inositol; gestational diabetes mellitus; myo-inositol

Introduction

Gestational diabetes mellitus (GDM) is a pregnancy complication defined as any degree of glucose intolerance with an onset during pregnancy [1]. It is a risk factor for women and offspring, including hypertensive disorders, cesarean section, fetal macrosomia, shoulder dystocia, neonatal hypoglycemia, and type 2 diabetes [2]. Identified risk factors for GDM include maternal age, maternal body mass index (BMI), ethnic background, family history, previous history of GDM, and previous/current adverse pregnancy outcome [1]. The prevalence of GDM varies widely depending on diagnostic method, study population, and screening criteria (universal or selective) [3].

Although the impact of GDM on maternal and fetal health has increasingly gained recognition, a consensus on the diagnostic methods and therapeutic approaches has not been reached. However, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated a correlation between early pregnancy fasting glucose levels and earlier onset of GDM [4]. Following the HAPO Study, the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) recommended new thresholds for the diagnosis of GDM [5].

Pregnancy is characterized by significant hormonal and metabolic maternal changes for ensuring adequate fetal nutrition [6]. Although insulin resistance

Contact Claudio Celentano celentanoclaudio70@gmail.com Department of Obstetrics and Gynecology, University of Chieti, via dei Vestini, Chieti 66100, Italy

with increasing of gestational age provides an improving glucose supply to the fetus, if this condition is not adequately balanced by insulin secretion due to increased beta-cell mass and response, it could contribute to a higher risk of developing GDM [7]. Recently, given the growing worldwide incidence of this complication and the increase in health care costs the need to determine shared effective strategies for the prevention, diagnosis, and management on GDM was reported [8].

Inositol, an insulin sensitizing agent, was reported to modulate insulin sensitivity in animal models and human conditions characterized by insulin resistance [9,10]. Recently, several authors reported that myo-inositol (MI) supplements improved maternal and fetal outcomes in patients at high risk for GDM compared to a control group treated only with dietary-control [10,11].

Different inositol stereoisomers, D-chiro-inositol (DCI), an inositol isoform synthesized by an epimerase that converts MI to DCI [12], were described as capable of influencing metabolism both alone [13] and when combined with MI [14,15].

The aim of this preliminary randomized, case-control, prospective clinical trial was to test the hypothesis that MI, DCI, or MI/DCI supplementations in pregnancy reduce the risk of developing GDM in a group of nonobese pregnant women with a high risk for this disorder.

Research design and methods

Study design and participants

The study design was a prospective, randomized, placebo-controlled single center clinical trial. The institutional review board (Department of Medicine and Ageing Science of the University "G. d'Annunzio" of Chieti-Pescara, Chieti, Italy) approved the project. The study was conducted according to the principles expressed in the Declaration of Helsinki, registered as Clinical Trial NCT01762826, and adhered to the CONSORT Statement [16]. All patients provided informed written consent prior to enrollment and randomization.

Consecutive singleton pregnant women attending our High-Risk Pregnancy Unit of the Hospital of University of "G. d'Annunzio" in Chieti from January 2012 to July 2017 upon referral for an elevated fasting glucose (glycemia $\geq$5.1 mmol/L or 92 mg/dL and $<$7.0 mmol/L or 126 mg/dL) at first trimester blood exams according to National Guidelines [17] were enrolled during their first visit. Pregnancies were dated by last menstrual period. A different gestational age was considered only if ultrasound scans did not confirm the last period within seven days during first trimester [18]. All subjects received information concerning the study protocol, indicating all possible risks and outcomes. If they accepted to participate they were randomly assigned to receive either inositol or placebo. Inositol group was divided into MI, DCI, or MI/DCI. Pregestational class II and III obesity (BMI above 35), patients younger than 18 years-old, multiple gestations, and pregestational diabetes were exclusion criteria.

Randomization and masking

All patients were informed of their hyperglycemic status, given dietary advice according to American Diabetes Association recommendations [19] and received counseling concerning physical activities they could safely perform [20,21]. Women were randomly assigned to the control or study groups using a 3:2:2:2 block design.

Risk factors for GDM such as first-degree relatives with type 2 diabetes, previous diagnosis of polycystic ovaries, previous GDM and macrosomic fetuses were recorded.

All women were routinely encouraged during their regular visits to follow the treatment program and asked if they were taking other dietary supplements, vitamins or medication to exclude the possibility that they were assuming inositol from other sources or other drugs that could have altered study results. At birth patients were asked to complete a questionnaire to confirm the regular assumption of inositol due to define the compliance.

Procedures

As per routine good clinical practice for the geographical area where this study was conducted, controls (C) were given 400 μg of folic acid orally per day. The MI group received 4000 mg myo-inositol plus 400 μg of folic acid per day for the entire period of pregnancy (divided in two sachets daily, taken with at least a 6-hour interval). The DCI group received 500 mg D-chiro-inositol plus 400 μg of folic acid per day in a single cap. The MI/DCI group received 27.6 mg D-chiro-inositol and 1100 mg myo-inositol per day (divided in two capsules daily, taken with at least a 6-hour interval). The MI, DCI, and MI/DCI dosages were determined from the results reported in previous studies evaluating insulin resistance during gestational diabetes [10,13].

The primary outcome was an abnormal maternal fasting oral glucose tolerance test (OGTT) at 24–28 weeks'

gestation, where either one or more blood glucose values were above the values of 5.1 mmol/L (92 mg/dL) at fasting, 10.0 mmol/L (180 mg/dL) at 1 hour, and 8.5 mmol/L (153 mg/dL) at 2 hours [4]. The secondary outcomes were if the patient required insulin therapy due to worsening altered glycemic values [22], maternal BMI increase (compared starting BMI to OGTT time), fetal growth at ultrasound scan (expressed as abdominal circumference percentile) [23], and occurrence of polyhydramnios (defined as amniotic fluid index above the 95th percentile) [24] at OGTT time, development of preeclampsia or pregnancy-induced hypertension, gestational age at birth, preterm delivery (expressed as number of patients delivered before 37 weeks' gestation completed), birthweight expressed as grams and percentile [25], route of delivery (expressed as cesarean section incidence), neonatal hypoglycemia (expressed as incidence of glucose values on neonate below 2.6 mmol/L) [26], and Neonatal Intensive Care Unit stay.

All patients underwent OGTT with 75 gm of glucose with 1-hour and 2-hour samplings between 24 and 28 weeks' gestation. At this time glycemic values, positivity at OGTT, gestational age, maternal BMI increase, fetal abdominal circumference percentiles, and occurrence of polyhydramnios (defined as amniotic fluid index above the 95th percentile) were recorded. Neonatal gender, birth weights expressed as grams and percentiles based on ethnic background, gestational age at birth, route of delivery, and neonatal hypoglycemia were recorded.

Statistical analysis

In order to permit the use of parametric statistical tests, a ratio of 3:2 (controls versus individual inositol formulation) was selected. This would also give a 1:2 ratio for controls versus a pool of all inositol formulations. Sample size calculation to detect a 50% reduction of the primary outcome, an incidence of abnormal maternal OGTT at 24–28 weeks' gestation (difference from a theoretical 65% in the control group to 32.5% in the inositol groups) based on a Type I Error (alpha) pf 0.05 and a Type II Error (beta) of 0.20 with a ratio of controls to subject of 3:2 indicated that 51 controls and 34 subjects per test group should be enrolled [11]. Considering a dropout and noncompliance with therapy rates between 15–20%, 60 women should be enrolled in the control group and 40 each treatment group.

The primary outcome was assessed with chi-squared test and Contingent cross-table, as appropriate. Secondary outcomes were evaluated with chi-squared test and Contingent cross table for nonparametric variables and *t*-test and ANOVA for parametric variables. The effect of BMI on the principle outcome measures was evaluated with a univariate analysis of Variance. The *p*-value was set at the two-sided significance level of .05. The relative risk (RR) with 95% confidence intervals (CI) was calculated for nonparametric parameters.

In order to evaluate the efficacy of each inositol stereoisomers supplementation on gestational diabetes mellitus, relative risk, and number needed to treat were calculated. Difference is efficacy between the study groups was assessed using the Non-Inferiority trial test.

Sample size and RR calculations were determined with MedCalc for Windows, version 11.4.2.0 (MedCalc Software, Mariakerke, Belgium). All other statistical analysis was performed with SPSS Statistics 24.0 (IBM, Armonk, NY).

Results

The enrollment period started on 1 January, 2012 and required four years to reach 180 consecutive women with gestational diabetes referred to our center due to an elevated blood glucose test whom met the inclusion/exclusion criteria and enrolled in the study (Figure 1). None of the women reported an adverse reaction to therapy. The compliance to therapy was evaluated from regular visits records with controls of capsule assumption and diaries, and postnatal questionnaire. If at least 80% of therapy was assumed then the patient was deemed compliant. Figure 1 is a CONSORT flow diagram indicating the patients lost to follow-up for noncompliance with therapy. The trial ended on the delivery date (October 2017) of the last enrolled participant. Four patients in C, one in DCI and two in MI/DCI had a spontaneous abortion after enrolling, and another subject had third trimester intrauterine fetal demise in DCI before OGTT ($p = .532$). The number of women who completed the follow-up period was 52, 39, 32, and 34, respectively. The groups did not present statistically significant differences for baseline maternal characteristics (Table 1).

The group of women allocated to receive myo-inositol alone had a significantly lower incidence of abnormal OGTT (5.1% (2/39) versus 61.5% (32/52) in C, 34.4% (11/32) in DCI, and 38.2% (13/34) in MI/DCI; $p < .001$). Nine women in the C group, one of the MI, five in DCI, three in MI/DCI required insulin treatment because they did not reach glycemic goals with diet alone [27]. Evaluation of the number of women who required insulin therapy for the four groups did not

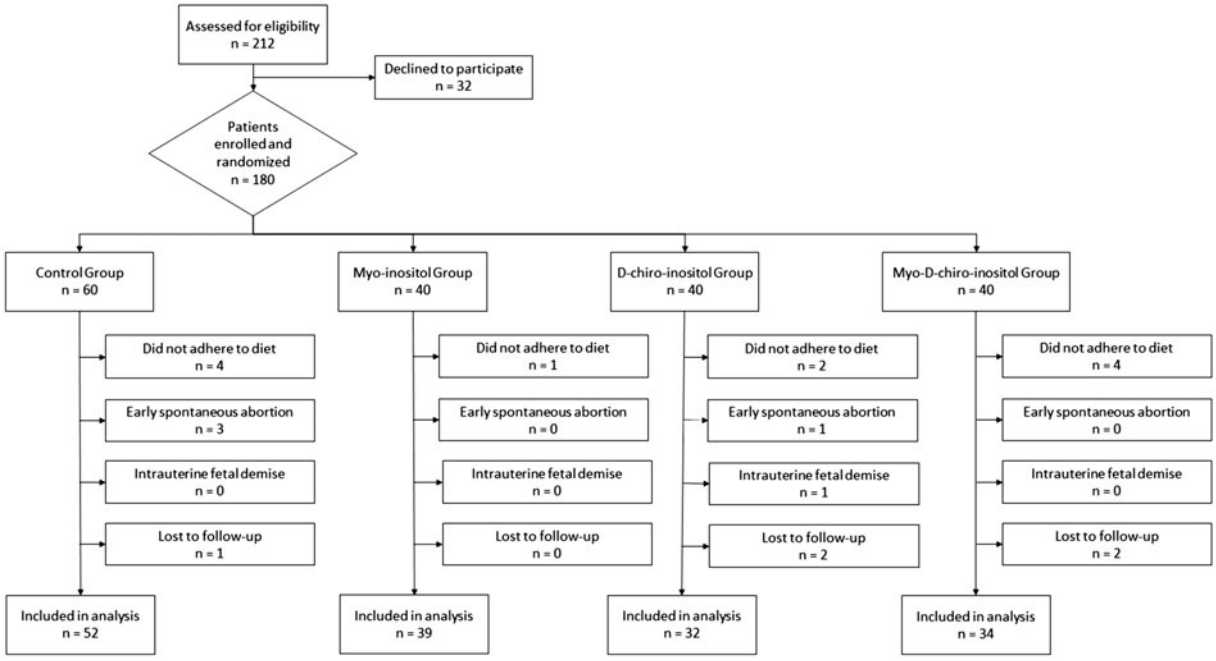

Figure 1. Participant flow chart.

Table 1. Baseline characteristics of the women at risk for GDM randomized to receive control treatment or inositols treatment.

Characteristic	C group	MI group	DCI group	MI/DCI group	Inositol groups ($n = 109$)	p	p
Maternal age (years)	33.9 ± 4.9	33.1 ± 4.9	34.4 ± 3.7	34.1 ± 4.2	33.8 ± 4.3	.604	.851
Number of pregnancies, *n* (%)						.627	.111
Nulliparous	32 (57.1)	26 (66.7)	20 (58.8)	21 (58.3)	67 (61.5)	.920	.993
One	17(30.4)	11 (28.2)	11 (32.4)	13 (36.1)	35 (32.1)	.887	.818
Two or more	7 (12.5)	2 (5.1)	3 (8.8)	2 (5.6)	7 (6.4)	.484	.159
Pre-gestational BMI (kg/m2)	24.4 ± 4.1	23.5 ± 3.4	24.4 ± 4.9	23.5 ± 4.6	23.8 ± 4.3	.627	.391
Additional risk factors *n* (%)	27 (48.2)	17 (43.6)	13 (38.2)	12 (34.3)	42 (38.9)	.577	.183
Obesity *n* (%)	2 (3.8)	1 (2.6)	3 (9.4)	3 (8.8)	7 (6.4)	.689	.490
Family history of DM2 *n* (%)	13 (25.0)	9 (23.1)	4 (12.5)	6 (17.6)	19 (17.4)	.862	.312
Previous GDM and or macrocosmic neonate *n* (%)	7 (12.5)	5 (12.8)	3 (9.4)	2 (5.6)	10 (9.2)	.708	.455
Previous PCOs *n* (%)	7 (12.5)	3 (7.7)	4 (11.7)	3 (8.8)	10 (9.2)	.823	.455
Gestational age at diagnosis (wks) [min–max]	12.7 ± 4.6 [7–20]	12.3 ± 3.7 [7–21]	12.4 ± 4.2 [7–19]	12.9 ± 3.2 [7–20]	12.5 ± 3.7 [7–21]	.901	.794
Fasting glucose (mmol/L)	5.4 ± 0.3	5.4 ± 0.3	5.3 ± 0.2	5.4 ± 0.3	5.4 ± 0.3	.296	.844

yield a statistically significant reduction of the relative risk ($p = .134$) (Table 2).

Basal, 1-hour, and 2 hours glycemic controls were significantly lower in exposed groups ($p < .001$, .011, and .037, respectively) (Figure 2 and Table 3). Abdominal circumference above 95th percentile at the time of OGTT was identified in one control fetus and in two fetuses exposed to D-chiro-inositol alone ($p = .610$) (Table 2). However, the mean abdominal circumference percentile in MI was significantly lower (42.6 ± 17.8 versus 61.5 ± 22.8 in C, 63.1 ± 19.5 in DCI, and 52.9 ± 17.5 in MI/DCI; $p < .001$) (Table 3). Polyhydramnios was reported in seven (13.5%) controls, in four exposed to D-chiro-inositol (12.5%), and in none in the MI and MI/DCI groups ($p = .182$). Incidence of preeclampsia and pregnancy-induced-hypertension occurred one in C, one in DCI and two in MC/DCI ($p = .102$) (Table 2).

Route of delivery, birth weight, and fetal gender did not present significant differences between groups, whereas the gestational age at delivery was significantly higher for the MI group. Preterm birth occurred in three controls, one MI and two MI/DCI ($p = .124$) (Table 2 and Table 3). The differences in birth weights was statistically significant when expressed as either grams ($p = .047$), or percentiles ($p < .001$). Neonatal birthweight above 4000 gm occurred in three controls and six cases exposed to inositols, one in MI, and five in MI/DCI ($p = .8651$). Furthermore, after birth, neonatal hypoglycemia was recorded in 11 in C, five in DCI, and three in MI/DCI

Table 2. Intention-to-treat analysis: Primary and non-parametric secondary outcomes in women at high risk for GDM randomized in C group ($n = 52$), or inositol treatment ($n = 105$) divided in MI ($n = 39$), DCI ($n = 32$), and MI/DCI ($n = 34$). Values reported as *n* (%).

Outcome	C group *n* (%)	MI group *n* (%)	DCI group *n* (%)	MI/DCI group *n* (%)	Inositols group *n* (%)	Cross-table (*p*)	Chi-squared (*p*)
Primary outcome							
Abnormal maternal OGTT	32/52 (61.5)	2/39 (5.1)	11/32 (34.4)	13/34 (38.2)	26/105 (24.8)	<.001	<.001
Secondary outcomes							
Insulin therapy	9/52 (17.3)	1/39 (2.6)	5/32 (15.6)	3/34 (8.8)	9/105 (8.6)	.134	.106
Fetal abdominal circumference above 95th percentile	1/52 (1.9)	0/39 (0)	2/32 (6.2)	0/34 (0)	2/105 (1.9)	.610	.994
Polyhydramnios	7/52 (13.5)	0/39 (0)	4/32 (12.5)	0/34 (0)	4/105 (3.8)	.182	.026
Route of delivery (Cesarean Section)	27/52 (51.9)	14/39 (35.9)	12/32 (37.5)	17/34 (50.0)	43/105 (40.9)	.380	.193
Pre-Eclampsia or pregnancy induced hypertension	1/52 (1.9)	0/39 (0)	1/32 (3.1)	2/34 (5.9)	3/105 (2.9)	.102	.727
Pre-term birth	3/52 (5.8)	1/39 (2.6)	0/32 (0)	2/34 (5.9)	3/105 (2.9)	.124	.370
Neonatal hypoglycemia	11/52 (21.1)	0/39 (0)	5/32 (15.6)	3/34 (8.8)	8/105 (7.6)	.023	.014
Neonatal Intensive Care Unit stay	2/52 (3.8)	0/39 (0)	1/32 (3.1)	2/34 (5.9)	3/105 (2.9)	.142	.739

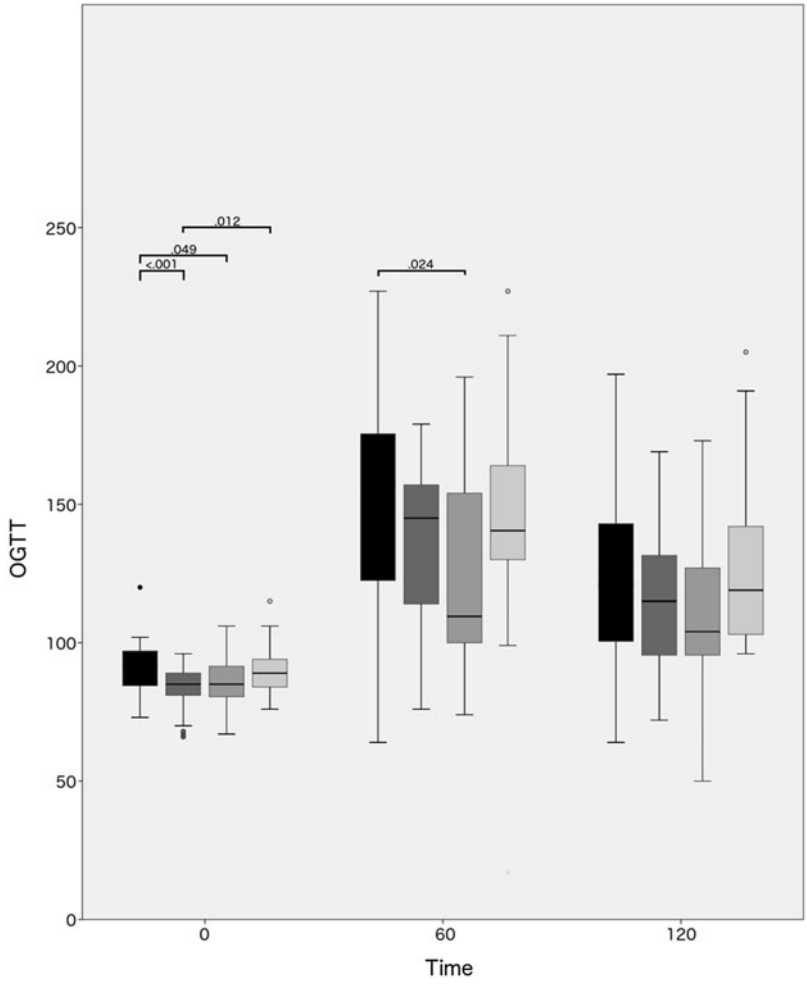

Figure 2. OGTT results.

whilst in no cases in the MI ($p = .023$). Neonatal Intensive Care Unit stay occurred in three cases of C, one of MI, and two MI/DCI ($p = .124$) (Table 2 and Table 3).

BMI had a statistically significant effect on all OGTT measurements (univariate analysis of variance; OGTT basal value $F(1152) = 710.01$, $p = .001$; OGTT at 1 hour $F(1,152) = 8303.45$, $p = .009$; OGTT at 2 hours

Table 3 Intention-to-treat analysis: Parametric secondary outcomes in women at high risk for GDM randomized in C group ($n = 52$), or inositol treatment ($n = 105$) divided in MI ($n = 39$), DCI ($n = 32$), and MI/DCI ($n = 34$). Values reported as mean ± standard deviation.

	Group						
Outcome	Control	Myo-inositol	D-chiro-inositol	Myo- D-chiro-inositol	Inositols	ANOVA (p)	t-test (p)
Secondary outcomes							
Gestational age at OGTT	26.9 ± 1.7	27.0 ± 1.2	27.3 ± 0.8	27.0 ± 1.6	27.1 ± 1.5	.627	.324
OGTT							
0 minutes	5.1 ± 0.5	4.7 ± 0.4	4.8 ± 0.5	5.0 ± 0.4	4.8 ± 0.4	<.001	.001
60 minutes	8.4 ± 2.1	7.5 ± 1.5	7.0 ± 2.0	8.1 ± 2.1	7.5 ± 3.4	.178	.017
120 minutes	7.0 ± 1.9	6.4 ± 1.4	6.1 ± 1.6	7.0 ± 1.6	6.5 ± 1.6	.086	.111
BMI increase	3.8 ± 2.4	2.3 ± 1.1	3.6 ± 1.4	2.7 ± 1.2	2.8 ± 1.3	<.001	<.001
Fetal abdominal circumference (percentiles)	61.5 ± 22.8	42.6 ± 17.8	63.1 ± 19.5	52.9 ± 17.5	52.2 ± 19.9	<.001	.010
Gestational age at delivery	38.1 ± 1.8	39.1 ± 1.7	38.9 ± 1.1	38.3 ± 1.8	38.8 ± 1.6	.025	.016
Birthweight (grams)	3361 ± 521	3238 ± 371	3552 ± 345	3223 ± 583	3360 ± 459	.047	.999
Birthweight (percentiles)	58.6 ± 20.1	43.1 ± 19.6	66.3 ± 27.9	65.1 ± 24.8	57.9 ± 25.8	<.001	.966
Large for gestational age (>90th percentiles)	3 (5.36%)	0 (0%)	4 (11.42%)	2 (5.71)	6 (5.66%)	.764	.988

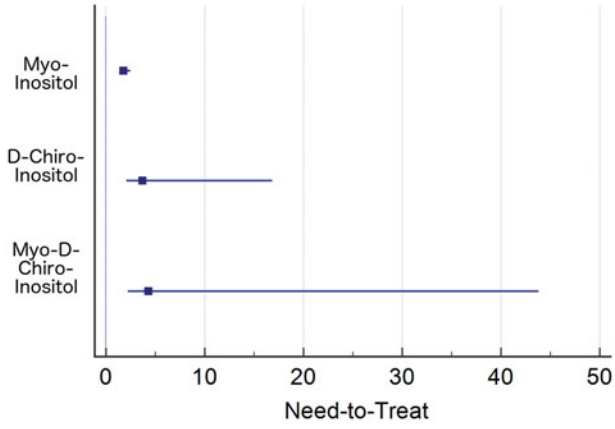

Figure 3. Number Needed-to-Treat.

F(1,152) = 14 152.31, $p < .001$; and positive OGTT F(1,152) = 5.347, $p = .022$), but not with the other principle outcomes including patients requiring insulin therapy.

The relative risk reduction related to primary outcome was 0.083, 0.559, and 0.621 for MI, DCI, and MI/DCI groups, respectively (Figure 2). The noninferiority outcomes confirmed superiority in responses in the MI and DCI groups, with a CI largely above the 25% of response only for the MI group. On the contrary, a statistically significant difference between MI/DCI was not observed. The "Number-Needed-to-Treat" benefits were 1.773, 2.175, and 4.291 for MI, DCI, and MI/DCI groups respectively (Figure 3), and thus better for the MI group.

Discussion

This is the first study that compared the different inositol stereoisomers available for use in pregnancy to prevent GDM in a single-center open-label randomized study. The results of this study were concordant with a previous study that reported that dietary myo-inositol treatment in GDM women significantly decreased third trimester and delivery signs of GDM [11]. Furthermore, the noninferiority analysis demonstrated the largest benefit in the myo-inositol group compared to D-chiro-inositol, while the combined drug was not inferior to controls. The relevance of our findings is mainly related to the possibility of an effective therapeutical approach in GDM using myo-inositol alone at a dosage of 4000 mg daily. The present study was consistent with previous studies in patients with PCOs and at high risk for GDM in which myo-inositol supplementation decreased insulin resistance [11,28]. Nestler et al. reported that D-chiro-inositol increased the sensitivity to insulin in disorders strongly associated with insulin resistance [29]. A subsequent study confirmed an active role of dietary myo-inositol in insulin resistance of GDM patients [27]. Recently, the combined administration of myo- and D-chiro-inositol was used in PCOs patients [30], and demonstrated its efficacy in insulin resistance management.

Unfer et al. recently reported the physiological ratio of inositol stereoisomers usually found in the human body [31]. The combination of MI/DCI in a 40:1 ratio was a novel approach to reproduce what naturally occurs *in vivo* and was used in gynecological patients [30] and in the prevention of GDM [32], with opposite results. However, no study to date has compared MI, DCI, and MI/DCI in terms of maternal and fetal/neonatal improvements.

On the other hand, contradictory results have been reported in obstetrics [15,32,33]. Malvasi et al. used the combined inositol stereoisomers (2000 mg/day

myo-inositol, 400 mg/day D-chiro-inositol, 400 μg/day folic acid, and 10-mg/day manganese) and demonstrated an improvement in glucose blood levels and lipid parameters in low-risk pregnant women [15]. The same group published preliminary data on resveratrol added to myo-inositol and D-chiro-inositol compared to MI/DCI on cholesterol triglycerides and glucose blood levels with a significant improve after 30–60 days in pregnant nonobese women [34]. Recently, Dell'Edera et al. reported a significant reduction in onset of GDM (5/40 versus 18/43; $p = .0028$) a group of pregnant women presenting glycemic values above 92 mg/dL (5.1 mmol/L), and similar results for the prevention of macrosomia (2/40 versus 11/43; $p = .0099$). The present study treated patients with 250 mg/day of D-chiro-inositol, 1750 mg/day of myo-inositol, 12.5 mg/day zinc, 10 mg/day methylsulfonylmethane and 400 mg/day of 5-methyl-tetrahydrofolic acid [33]. A larger study did not report similar results for the prevention of GDM using myo-inositol and D-chiro-inositol in a 40:1 ratio with a dosage of 1100 mg MI, 27.6 mg DCI and 400 μg folic acid daily [32]. These differences could be attributed to the different dosage and/or synergic action of anti-inflammatory agents recently added in many inositol suppliers.

Previous data demonstrated a greater decrease in markers for insulin resistance among gestational diabetic women with dietary supplementation randomly exposed to myo-inositol plus folic acid as compared with folic acid alone in high risk patients [11,35,36].

Although the biochemical mechanism for reported benefits of oral administration of myo-inositol on metabolism of patients with GDM and other states of insulin resistance are still unknown, it is possible that it derives from an intracellular effect directly on the activation of acetyl CoA carboxylase-stimulating lipogenesis or as a precursor of D-chiro-inositol containing inositol phosphoglycan, which is bound to the extracellular matrix of the cells. It was hypothesized that the binding of insulin to specific receptors stimulates D-chiro-inositol containing inositol phosphoglycan transport intracellularly [37], and explains a role as mediator in the insulin-signaling cascade [27].

Oral myo-inositol seems to be an insulin-sensitizing factor. It was reported to reduce plasma glucose levels in insulin resistance conditions such as polycystic ovary syndrome [37] and during the third trimester of GDM pregnancies [38]. The lack of international uniformity for the diagnosis and treatment of GDM was initially addressed by HAPO study results [4]. All pregnant women underwent fasting glucose screening during the whole pregnancy increasing the rate of GDM diagnosis. Different applications of screening guidelines were suggested [2].

In our study the direct effect of inositol dietary exposure on second and third trimester findings was defined as incidence of GDM and necessity of insulin therapy [3,5,8]. Furthermore, neonatal outcomes demonstrated a greater gestational age at delivery due to the management of healthy fetuses at term and post-term deriving from the reduction of adverse obstetric findings during third trimester due to overt diabetes [39]. In GDM the appropriate timing of delivery should be based on both maternal and fetal risk factors. In general, delivery can be delayed until term or until the spontaneous onset of labor as long as a good metabolic control and adequate antenatal surveillance are maintained [8]. In patients with poorly controlled GDM, however, delivery as soon as pulmonary maturity is documented is recommended [8]. In the MI group, in fact, the good metabolic control was reflected by later gestational age at delivery and lower birthweight. Furthermore, the GDM well controlled in exposed groups was supported by lower incidence of neonatal hypoglycemia.

Calculating the Relative Risk and "Number Needed-to-Treat", MI group presented the best result of 1.77 (Figure 3). MI had also the best efficacy as drug, even though DCI did not demonstrate "Non-Inferiority" as drug (Figure 4). Otherwise, MI/DCI group had a Relative Risk of 0.621 with a wider 95% CI (0.385–1.002).

Univariate analysis of variance confirmed a significant correlation of pregestational BMI to OGTT results, even if previous reported results [40] did not demonstrate a significative correlation with the requirement of insulin therapy.

The main weakness of this study was that the evaluation of GDM obstetric adverse outcomes such as perinatal death, macrosomia, shoulder dystocia, bone fractures, nerve palsy, elective cesarean, early delivery, and emergency cesarean section would require a larger study population. A major difficulty can be found in absence of stratification of risk deriving from the value of fasting glucose. The study was planned after publication of HAPO study and the cut-off value of 92 mg% (5.1 mmol/L) was taken into account. Latter the National Guidelines and suggestions from Scientific Societies [17] considered differently the population above 95 mg% [39] and further studies demonstrated that the risk of gestational diabetes mellitus can be considered for fasting values above 100 mg% [38]. Also, not using a correction for multiple comparisons increases the risk of type one

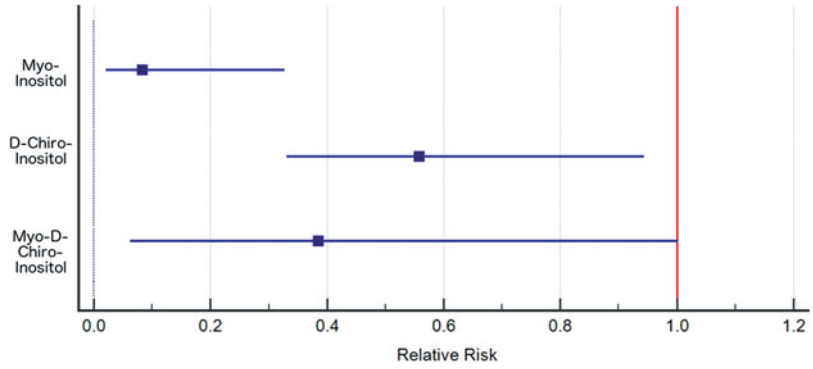

Figure 4. Non Inferiority.

errors. But this choice is supported by the results in which all statistically significant results indicated the same correlation. Also, this should be conducted in a multicenter study with a larger study population in order to adequately evaluate the risk of adverse effects in this high-risk group.

In conclusion, our study confirmed the efficacy of inositol supplementation in pregnant women at risk for GDM, and demonstrated that the three formulations study was similar in terms of efficacy but that the MI formulation presented a lower relative risk for an abnormal maternal OGTT.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Claudio Celentano http://orcid.org/0000-0003-4976-2957
Barbara Matarrelli http://orcid.org/0000-0001-8699-9035
Giulia Pavone http://orcid.org/0000-0002-5018-8043
Ester Vitacolonna http://orcid.org/0000-0003-1756-661X
Peter A. Mattei http://orcid.org/0000-0002-7343-5625
Vincenzo Berghella http://orcid.org/0000-0003-2854-0239
Marco Liberati http://orcid.org/0000-0001-7034-0973

References

[1] Buchanan TA, Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005;115(3):485–491.
[2] Teh WT, Teede HJ, Paul E, et al. Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. Aust N Z J Obstet Gynaecol. 2011;51(1):26–30.
[3] Ryan EA. Diagnosing gestational diabetes. Diabetologia. 2011;54(3):480–486.
[4] The HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcome (hapo) study: associations with neonatal anthropometrics. Diabetes. 2009;58(2):453–459.
[5] Coustan DR, Lowe LP, Metzger BE. The hyperglycemia and adverse pregnancy outcome (HAPO) study: can we use the results as a basis for change? J Matern Fetal Neonatal Med. 2010;23(3):204–209.
[6] Bozzetti P, Ferrari MM, Marconi AM, et al. The relationship of maternal and fetal glucose concentrations in the human from midgestation until term. Metabolism. 1988;37(4):358–363.
[7] Phelps RL, Metzger BE, Freinkel N. Carbohydrate metabolism in pregnancy. XVII. Diurnal profiles of plasma glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. Am J Obstet Gynecol. 1981;140(7):730–736.
[8] Chiefari E, Arcidiacono B, Foti D, et al. Gestational diabetes mellitus: an updated overview. J Endocrinol Invest. 2017;40(9):899–909.
[9] Larner J, Brautigan DL, Thorner MO. D-chiro-inositol glycans in insulin signaling and insulin resistance. Mol Med. 2010;16(11–12):543–552.
[10] Corrado F, D'Anna R, Di Vieste G, et al. The effect of myo-inositol supplementation on insulin resistance in patients with gestational diabetes. Diabet Med. 2011;28(8):972–975.
[11] Matarrelli B, Vitacolonna E, D'Angelo M, et al. Effect of dietary myo-inositol supplementation in pregnancy on the incidence of maternal gestational diabetes mellitus and fetal outcomes: a randomized controlled trial. J Matern Fetal Neonatal Med. 2013;26(10):967–972.
[12] Pak Y, Huang LC, Lilley KJ, et al. In vivo conversion of [3H]myoinositol to [3H]chiroinositol in rat tissues. J Biol Chem. 1992;267(24):16904–16910.
[13] Pizzo A, Laganà AS, Barbaro L. Comparison between effects of myo-inositol and D-chiro-inositol on ovarian function and metabolic factors in women with PCOS. Gynecol Endocrinol. 2014;30(3):205–208.
[14] Colazingari S, Treglia M, Najjar R, et al. The combined therapy myo-inositol plus D-chiro-inositol, rather than D-chiro-inositol, is able to improve IVF outcomes: results from a randomized controlled trial. Arch Gynecol Obstet. 2013;288(6):1405–1411.
[15] Malvasi A, Casciaro F, Minervini MM, et al. Myo-inositol, D-chiro-inositol, folic acid and manganese in second trimester of pregnancy: a preliminary investigation. Eur Rev Med Pharmacol Sci. 2014;18(2):270–274.
[16] Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

[17] Conferenza Nazionale di Consenso per Raccom andazioni ed implementazione delle nuove linee guida per lo screening e la diagnosi del diabete gestazionale (GDM). Available from: http://www.sibioc.it/materiale/Documento_Finale_Consensus_Naz_GDM_afterAM2.pdf; 2010.

[18] Pexsters A, Daemen A, Bottomley C, et al. New crown-rump length curve based on over 3500 pregnancies. Ultrasound Obstet Gynecol. 2010;35(6):650–655.

[19] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2008;31: S55–SS60.

[20] Ha V, Bonner AJ, Jadoo JK, et al. The effects of various diets on glycemic outcomes during pregnancy: a systematic review and network meta-analysis. PLOS ONE. 2017;12(8):e0182095.

[21] Russo LM, Nobles C, Ertel KA, et al. Physical activity interventions in pregnancy and risk of gestational diabetes mellitus: a systematic review and meta-analysis. Obstet Gynecol. 2015;125(3):576–582.

[22] Kelley K, Carroll D, Meyer A. A review of current treatment strategies for gestational diabetes mellitus. DIC;4:1–15.

[23] Paladini D, Rustico M, Viora E, et al. Fetal size charts for the Italiana population. Normative curves of head, abdomen and long bones. Print Dig. 2005;25:456–464.

[24] Rutherford SE, Phelan JP, Smith CV, et al. The four-quadrant assessment of amniotic fluid volume: an adjunct to antepartum fetal heart rate testing. Obstet Gynecol. 1987;70(3 Pt 1):353–356.

[25] Festini F, Procopio E, Taccetti G, et al. Birth weight for gestational age centiles for Italian neonates. J Matern Fetal Neonatal Med. 2004;15(6):411–417.

[26] Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127(3):575–579.

[27] Baillargeon JP, Iuorno MJ, Apridonidze T, et al. Uncoupling between insulin and release of a D-chiro-inositol-containing inositolphosphoglycan mediator of insulin action in obese women with polycystic ovary syndrome. Metab Syndr Relat Disord. 2010;8(2):127–136.

[28] D'Anna R, Di Benedetto V, Rizzo P, et al. Myo-inositol may prevent gestational diabetes in PCOS women. Gynecol Endocrinol. 2012;28(6):440–442.

[29] Nestler JE, Jakubowicz DJ, Reamer P, et al. Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome. N Engl J Med. 1999;340(17):1314–1320.

[30] Nordio M, Proietti E. The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. Eur Rev Med Pharmacol Sci. 2012;16(5):575–581.

[31] Unfer V, Porcaro G. Updates on the myo-inositol plus D-chiro-inositol combined therapy in polycystic ovary syndrome. Expert Rev Clin Pharmacol. 2014;7(5):623–631.

[32] Farren M, Daly N, McKeating A, et al. The prevention of gestational diabetes mellitus with antenatal oral inositol supplementation: a randomized controlled trial. Diabetes Care. 2017;40(6):759–763.

[33] Dell'Edera D, Sarlo F, Allegretti A, et al. The influence of D-chiro-inositol and D-myo-inositol in pregnant women with glucose intolerance. Biomed Rep. 2017;7(2):169–172.

[34] Malvasi A, Kosmas I, Mynbaev OA, et al. Can trans resveratrol plus D-chiro-inositol and myo-inositol improve maternal metabolic profile in overweight pregnant patients? Clin Ter. 2017;168(4):e240–ee247.

[35] D'Anna R, Scilipoti A, Giordano D, et al. Myo-inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. Diabetes Care. 2013;36(4):854–857.

[36] D'Anna R, Di Benedetto A, Scilipoti A, et al. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women: a randomized controlled trial. Obstet Gynecol. 2015;126(2):310–315.

[37] Saltiel AR. Second messengers of insulin action. Diabetes Care. 1990;13(3):244–256.

[38] Corrado F, D'Anna R, Cannata ML, et al. Correspondence between first-trimester fasting glycaemia, and oral glucose tolerance test in gestational diabetes diagnosis. Diabetes Metab. 2012;38(5): 458–461.

[39] Wier LM, Witt E, Burgess J, et al. Hospitalizations related to diabetes in pregnancy, 2008. In: Statistical Brief #102. Rockville (MD): Agency for Healthcare Research and Quality (US); 2010. Available from: https://www.ncbi.nlm.gov/books/NBK52649/.

[40] Zhang Y, Shao J, Li F, et al. Factors in Gestational diabetes mellitus predicting the needs for insulin therapy. Int J Endocrinol. 2016;2016:4858976.