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STUDIES IN HUMANS

Myo-inositol supplementation to prevent gestational diabetes in overweight non-obese women: bioelectrical impedance analysis, metabolic aspects, obstetric and neonatal outcomes – a randomized and open-label, placebo-controlled clinical trial

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ABSTRACT

This study aims to evaluate the effects of myo-inositol supplementation on gestational diabetes mellitus (GDM) rates and body water distribution in overweight non-obese women. 223 overweight non-obese women pregnant were randomly assigned to the treatment group (2 g of myo-inositol plus 200 µg of folic acid) or to the placebo one (200 µg of folic acid). The treatment lasted until three weeks after delivery. A tetrapolar impedance analyser was used to study body composition. The incidence of GDM was significantly reduced in the myo-inositol group compared with the placebo group. There was a significant increase in TBW, ECW and ICW values in the placebo group compared to the myo-inositol group. We have recorded a significant reduction in the overall incidence of pregnancy-induced hypertension in the myo-inositol group compared with the placebo group. Our results demonstrate the effectiveness of myo-inositol supplementation in preventing GDM in overweight non-obese pregnant women.

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Gestational diabetes mellitus; myo-inositol; body water; pregnancy; outcomes

Introduction

Gestational diabetes mellitus (GDM) can be defined as "any degree of glucose intolerance" with onset or "first recognition during pregnancy" (Metzger et al. 2007).

The development of GDM is associated with a variety of risk factors, more specifically body weight which is among the most important ones for gestational diabetes (Imam 2013); indeed, body mass index (BMI) ranging 25.1–29.9 predisposes not only to GDM but also to several adverse outcomes in pregnancy (Corrado et al. 2014; Zhang et al. 2014).

Despite a general agreement on its definition, there is no universal consensus on the diagnostic criteria of GDM throughout the last 50 years. O'Sullivan firstly proposed a two-step approach using a glucose challenge test (GCT) (50 g–1 h), followed by an oral glucose tolerance test (OGTT) (100 g–3 h) if the result of the GCT is higher than the cut-off considered (O'Sullivan and Mahan 1964). Any amount of abnormal values higher than two during the assessment of the OGTT had been deemed diagnostic for gestational diabetes (O'Sullivan and Mahan 1964; O'Sullivan et al. 1973). This approach, later modified by the National Diabetes Data Group (NDDG) (Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. National Diabetes Data Group (1979) and Carpenter (Carpenter and Coustan 1982), was the most considered in Western countries until 8 years ago, when the International Association of Diabetes and Pregnancy Study Groups (IADPSG) Consensus Panel (Metzger et al. 2010), on the basis of the HAPO study results (Metzger et al. 2008), recommended new diagnostic criteria. At first, they proposed evaluating the first trimester fasting glycaemia to exclude cases of pre-existing diabetes ($\geq$126 mg/dl), and then suggested that a 75 g–2 h OGTT should be undergone by all pregnant women in their 24th–28th week of gestation, with just one value of abnormal plasma glucose being enough to

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diagnose GDM (fasting $\geq$ 92 mg/dl; 1 h $\geq$ 180 mg/dl and 2 h $\geq$ 153 mg/dl) (Metzger et al. 2010).

However, the Italian Institute of Health in the Guidelines of Physiological Pregnancy (2011) advised that only pregnant women with a defined risk factor ought to take part in an OGTT (Sistema Nazionale Linee Guida – Istituto Superiore di Sanità 2011). It is, in fact, highlighted that screening only patients with at least one risk factor could make the diagnosis of GDM more cost-effective; the limit of this approach, based on a narrow vision of costs and benefits, is the possibility of determining a misconception with consequent under-treatment of patients with carbohydrate intolerance.

Therapeutic approaches to GDM include medical nutrition therapy (MNT) and weight management, physical exercise, self-monitoring of blood glucose (SMBG), and pharmacological therapy, if required (Kim 2010; Mirghani Dirar and Doupis 2017).

In recent years, a vast array of studies has been conducted on the effectiveness of substances such as myo-inositol for the prevention of GDM and related complications (Brown et al. 2016; Santamaria et al. 2018). Myo-inositol is an isomer of inositol, a simple carbohydrate and nutrient which has an essential role for many cell functions (Croze and Soulage 2013). It is naturally present in fresh fruit and vegetables, cereals, legumes and nuts, but it is also synthesised by our body, especially in the liver (Clements and Darnell 1980; Genazzani et al. 2008). Although its therapeutic effects have been widely demonstrated by numerous studies (Genazzani et al. 2008; Croze and Soulage 2013), it is commonly available on the market as a dietary supplement, in water-soluble powder form or capsules (Brown et al. 2016).

Recent studies by D'Anna et al. demonstrated that diet supplementation with myo-inositol has insulin-sensitizing effects and may decrease GDM occurrence in populations at risk for this disease, like obese women or women with family history for Diabetes Mellitus type 2 (T2DM) (Corrado et al. 2011; D'Anna et al. 2013, 2015; Santamaria et al. 2016).

Maternal body composition experiences profound adaptive changes during pregnancy (Ghezzi et al. 2001). Fat mass (FM), fat-free mass (FFM) and total body water (TBW) increase with different modes, and their effects on pregnancy outcomes represent a very interesting field for perinatal medicine, which is currently investigated in a fragmentary and non-homogeneous manner (Larciprete et al. 2003).

Different techniques for measuring body composition are available, but one of the most used in clinical practice is bioelectrical impedance analysis (BIA). BIA is a method used to test body composition, which is simple and reproducible. It is a relatively recent technique that has found a clinical application only since the 1980s thanks to the development of portable analysers (RJL Systems in USA/Akern Srl in Italy), which operated similarly to the electrocardiograph. Currently, the most adopted technique is based on the use of cutaneous electrodes used for ECG and positioned in two pairs (hand-foot tetrapolar technique). This technique allows measurements to be performed quickly, non-invasively, harmlessly, repeatedly, and at low cost (Heymsfield et al. 1996; Lukaski 1996).

Although several scientific works support the use of BIA in the study of some pathologies of pregnancy, such as gestational hypertension, pre-eclampsia and pregnancy hyperemesis (Valensise et al. 2000; Tazegül Pekin et al. 2015; Staelens et al. 2016), there are few actual data concerning the study of gestational diabetes and its correlation with body composition investigated through this well-established technique.

In the light of these considerations, the main objective of this study is to evaluate the occurrence of GDM and body water distribution in overweight non-obese pregnant women, randomised to a myo-inositol oral formulation (2 g myo-inositol + 200 µg folic acid) or placebo (200 µg folic acid). The secondary one is to evaluate the effects of treatment on the metabolism of these women, as well as on obstetric and neonatal outcomes.

Material and methods

Patients and study design

This prospective, randomised, open-label, placebo-controlled study was performed in a cohort of pregnant women enrolled at the Unit of Gynaecology and Obstetrics of the Department of Human Pathology in Adulthood and Childhood "G. Barresi," University of Messina, Italy. The trial is registered with the number NCT01047982 and was approved by the Ethical Committee of Messina University Hospital (E347/2008).

The enrolment started at the beginning of 2016 and lasted 2 years. Women were eligible if they met the following inclusion criteria: pre-pregnancy BMI $>$ 25 and $<$ 30 kg/m^2, first-trimester fasting plasma glucose $\leq$126 mg/dl and/or random glycaemia $<$200 mg/dl, single pregnancy, and Caucasian ethnicity. We excluded women who had a pre-pregnancy BMI $<$25 and $\geq$ 30 kg/m^2, previous GDM, pre-gestational diabetes, first-trimester glycosuria, and in treatment with

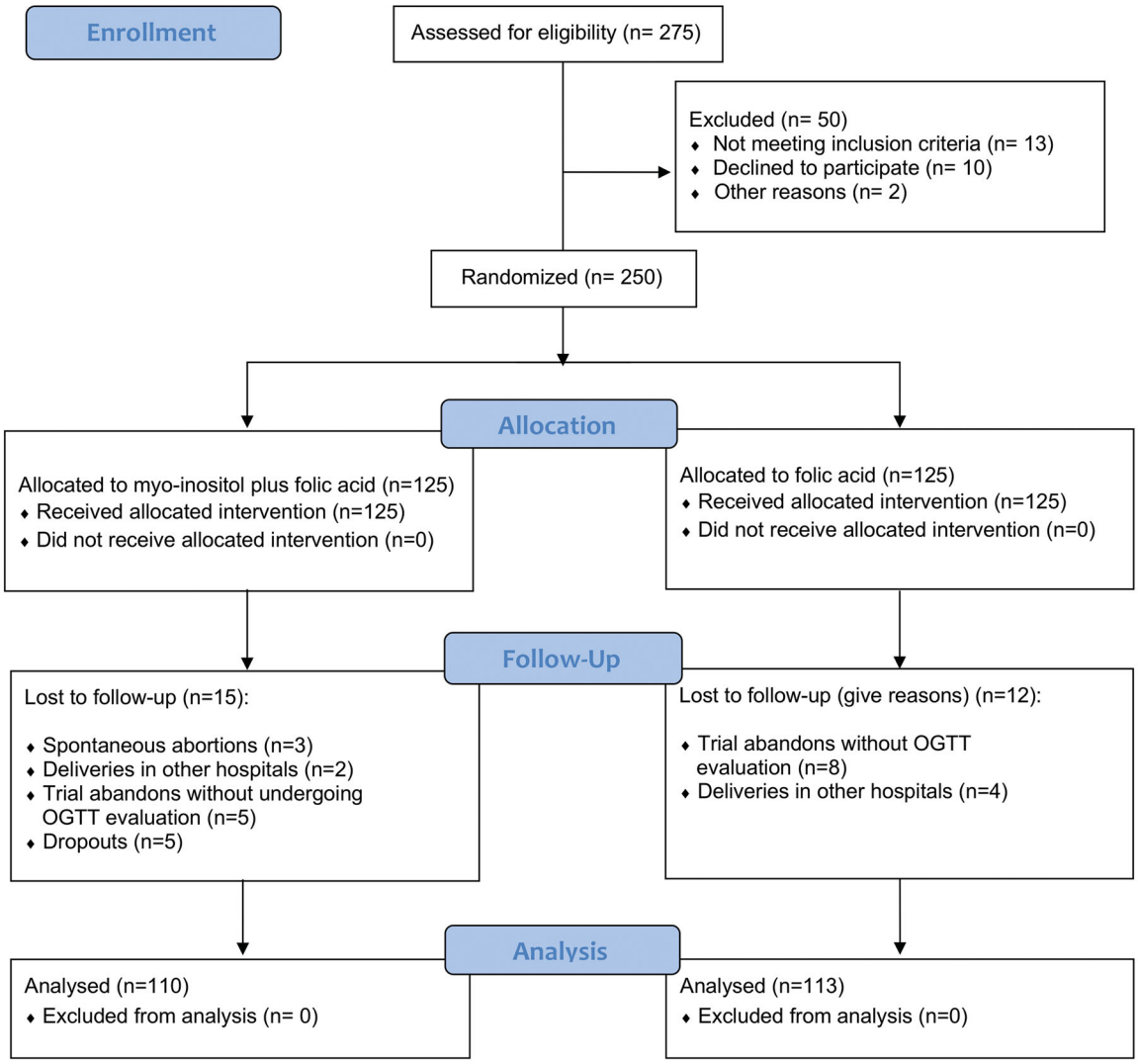

Figure 1. CONSORT flow diagram.

corticosteroids. A total of 275 Caucasian pregnant women were assessed for eligibility. Figure 1 shows the CONSORT flow diagram of the study.

Primary outcomes of interest in this study were the occurrence of GDM and body water distribution. Furthermore, changes in lipid metabolism (total cholesterol, HDL, LDL and triglycerides serum levels), prevalence of foetal macrosomia (foetal birth weight >4500 g at delivery), rate of caesarean section in emergency, preterm delivery (<37 weeks), Pregnancy Induced Hypertension (PIH) and preeclampsia were considered as secondary outcomes, also considering the occurrence of shoulder dystocia, neonatal hypoglycaemia as well as the need for transfer to the Neonatal Intensive Care Unit (NICU).

According to the recommendations of the IADPSG panel, a 75 g–2 OGTT was performed on all patients between the 24th and 28th weeks of gestation. We detected both the risk factors and the fasting glycaemia during the first trimester. The identification of risk factors was assessed following the recommendations of the National Institute of Health: age, BMI, family history of diabetes (especially in first-degree relatives), previous GDM, or previous macrosomia (birth weight > 4500 g).

GDM was diagnosed based on the following cut-off glycaemia values during OGTT: fasting $\geq$ 92 mg/dl; 1-h $\geq$ 180 mg/dl; 2-h $\geq$ 153 mg/dl.

The diagnosis of pregnancy-induced hypertension, without proteinuria, was made in the presence of 2 consecutive, traditional sphygmomanometric measurements of diastolic blood pressure $\geq$ 90 mm Hg and systolic blood pressure $\geq$ 140 mm Hg after the 20th week of pregnancy. Preeclampsia was diagnosed with two consecutive measurements of diastolic blood pressure $\geq$ 90 mm Hg and systolic blood pressure $\geq$ 140 mm Hg with urinary protein $\geq$ 300 mg/day, both after the 20th week of pregnancy.

At the time of the recruitment (12th–13th week), after providing written informed consent, all the eligible women who accepted to participate in the study were randomly assigned to one of the two groups. The treatment group received myo-inositol plus folic acid (2 g plus 200 µg twice/day—Inofolic®; Loli Pharma, Rome, Italy) while the placebo group received folic acid only (200 µg twice/day). The treatment lasted until three weeks after delivery. Besides, all patients followed the same diet according to the ADA recommendations.

A computer-generated random sampling method with a 1:1 ratio was used. A nurse sealed and randomly numbered the allocations in white envelopes according to the computer-generated scheme. After the eligibility assessment, 250 women were recruited for randomisation. The study design established that the gynaecologist knew the assignment of each patient.

Study measurements

At enrolment, Homeostasis Model Assessment-Insulin Resistance index (HOMA-IR) was evaluated through the assessment of fasting glucose and insulin levels, using an ELISA commercial kit (DRG Diagnostics, Marburg, Germany) to measure serum insulin, with the concentrations expressed in mIU/ml.

A tetrapolar impedance analyser (BIA 450 Bioimpedance Analyser; ESCO S.r.l., Rho, Italy) was utilised to study body composition and determine resistance (R, Ω) and reactance (Xc, Ω). Each woman was clothed but without shoes and socks, and lay supine on a non-conducting table, with the limbs distanced from the body and the legs separated from one another in a straight position. Tetrapolar electrode followed its standard placement, attaching the receiving electrodes at the dorsal surfaces of the right hand and foot and placing the sensing electrodes at the distal end of the metacarpal and metatarsal-phalangeal joints.

The applied current was 800 µA and was transmitted in a frequency of 50 kHz at the distal electrodes of the hand and foot; the voltage drop across the pregnant women was detected with the proximal electrodes. The examination lasted approximately 3 min.

According to the indications of Lukasky and Bolonchuk (Lukaski and Bolonchuk 1988) and Segal et al. (1987), height^2/resistance (cm^2/Ω) and height^2/reactance (cm^2/Ω) (bioelectrical impedance indices) were calculated in order to assess TBW, ECW, and ICW amounts.

Hematochemical assays, anthropometric and single-frequency bioimpedance measurements were performed at 12th/13th week of pregnancy (baseline, T0), 26th/27th week of pregnancy (T1), 31st/32nd week of pregnancy (T2) and 3 weeks after delivery (T3).

Sample size calculation

A sample size of 220 (110 for each treatment group) achieves 90% power, with an alpha value equal to 5%, to detect the same effect size of GDM incidence described by Santamaria et al. (Santamaria et al. 2016) and an ECW reduction of 1.9 kg, as reported by Larciprete et al. (Larciprete et al. 2003), assuming a compound symmetry covariance structure in a longitudinal study with 4 repeated measurement.

Statistical analysis

This trial used a protocol treatment analysis. Mean ± SD and percentages for continuous and categorical variables were used in order to report patients' characteristics at the baseline. Differences between continuous variables across treatment groups were evaluated by unpaired Student *t*-test or one-way ANOVA when appropriate. Categorical variables distribution was compared between groups by χ^2 test.

Univariate and multivariate logistic and longitudinal linear regression analyses were used to assess the effect of myo-inositol treatment on binary (i.e. GDM incidence) and continuous outcomes (i.e. ECW reduction), respectively.

There were adjustments made for multivariable analyses for age and smoke (as general confounders), adiposity measures (i.e. BMI), familiarity of type 2 diabetes, prior preeclampsia and gestational hypertension, hypertension or preeclampsia during current pregnancy, polycystic ovary syndrome, history of recurrent miscarriage and foetal macrosomia (as GDM-related confounders), first pregnancy, family history of type 2 diabetes and hypertension, previous obstetrical preeclampsia history, pre-existing hypertension and hereditary thrombophilia (as gestational hypertension-related confounders) and ongoing treatments (as anti-hyperglycemia and anti-hypertension). Odds Ratios (ORs) and beta values were used to report results, along with their 95% confidence intervals (CIs), when appropriate and a p-value < 0.05 was regarded as statistically significant. SAS Software, Release 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analyses.

Results

The recordings in the myo-inositol group registered three spontaneous abortions, two deliveries in other

hospitals, and five trial abandons without undergoing OGTT evaluation. Moreover, there were five dropouts, leaving 110 women for the analysis. No women reported any treatment-related side effects.

In the placebo group, the record counted eight trial abandons without OGTT evaluation and four deliveries in other hospitals, with a final group of 113 women for the analysis.

The two groups were similar for maternal age, pre-pregnancy BMI, spontaneous abortions, family history of type 2 DM and preeclampsia, percentage of smokers, nulliparous women, pre-existing hypertension, PCOS, and macrosomia. Table 1 summarises the main characteristics of the study population at baseline. At enrolment, the two groups also showed similar values for both hematochemical and body impedance measurements (Table 2).

The global incidence of GDM was significantly reduced in the myo-inositol group ($n = 9$, 8.2%) compared with the placebo group ($n = 24$, 21.2%) ($p = 0.006$). After adjustment for general confounders and adiposity measures, the placebo group was associated with an increased and significant GDM risk [OR 3.74 (95% CI 1.67–8.39; $p = 0.0014$)]. Similar results were found for GDM-related confounders, gestational hypertension-related confounders, and ongoing treatment adjustments. There were no findings for considerable differences in glycaemia at the different OGTT steps between myo-inositol and placebo groups, while a significant one in weight gain at OGTT was recorded (Table 3).

Both in the placebo group and the myo-inositol one, all women diagnosed with GDM (33) were treated with diet during pregnancy. However, among these patients, 18 women in the placebo group and seven women in the myo-inositol group needed a concomitant treatment with insulin at 26th/27th week, while 18 and 9 women in the placebo and myo-inositol group respectively, have been subjected to insulin therapy at 31st/32nd week. Instead, at clinical examination three weeks after delivery, 13 women in the placebo group and one woman in the myo-inositol group needed insulin to maintain the euglycemic state.

Among the most interesting results deriving from the evaluation of body composition through bioimpedance analysis, we note the decrease in the mean values of the FFM/FM ratio in the placebo group compared to the myo-inositol group in all the follow-up considered. This decrease was found to be significant at the follow-up performed at the third trimester of pregnancy (T2, 31st/32nd week) and at that performed three weeks after delivery (T3). In addition to the decrease in the mean values of the FFM/FM ratio, which is correlated with a more significant increase in FM, a worsening of the lipid panel (HDL, LDL, total cholesterol, and triglycerides) was also found in the placebo group at all the follow-up considered. However, these changes were not significant either in the gestational period (T0, T1, and T2) or in the post-gestational one (T3) (Table 4).

Table 5 reports the results about the role of the myo-inositol on the body water distribution, the

Table 1. General characteristics of the study groups at baseline.

	Myo-inositol ($n = 110$)	Placebo ($n = 113$)	p Value
Age (years)	27.18 ± 6.03	27.95 ± 4.90	0.2986
Nulliparous	51 (46.36)	52 (46.02)	0.9587
Pre-pregnancy weight (Kg)	69.67 ± 6.82	69.58 ± 4.89	0.9111
Pre-pregnancy BMI (Kg/m^2)	27.00 ± 1.49	26.68 ± 1.56	0.1186
Family history of DM II	36 (32.73)	42 (37.17)	0.4869
Family history of preeclampsia	3 (2.72)	3 (2.65)	0.9733
Smokers	6 (5.45)	5 (4.42)	0.7226
Pre-existing hypertension	1 (0.91)	1 (0.88)	0.9848
Hereditary thrombophilia	5 (4.55)	5 (4.42)	0.9653
PCOS	11 (10)	12 (10.62)	0.8791
Spontaneous abortions	41 (37.27)	34 (30.09)	0.2563
Macrosomia	10 (9.09)	8 (7.08)	0.5815

BMI: body mass index; DM II: diabetes mellitus type II; PCOS: polycystic ovary syndrome; IUGR: intrauterine growth restriction; PTD: preterm delivery. Data are reported as mean ± DS.

Table 2. Hematochemical and bioimpedance measurements of the two groups at baseline.

	Myo-inositol ($n = 110$)	Placebo ($n = 113$)	p Value
Total cholesterol (mg/dl)	163.06 ± 26.22	162.74 ± 32.78	0.9432
HDL (mg/dl)	49.64 ± 6.98	50.56 ± 6.70	0.3157
LDL (mg/dl)	93.64 ± 26.73	92.73 ± 32.30	0.818
Triglycerides (mg/dl)	98.74 ± 29.81	97.29 ± 38.40	0.7544
Fasting Glucose (mg/dl)	82.20 ± 12.12	83.10 ± 14.10	0.6113
Fasting Insulin (mU/ml)	9.50 ± 2.55	10.00 ± 2.21	0.119
HOMA-IR	1.96 ± 0.76	2.10 ± 0.77	0.1916
TBW (L)	45.61 ± 4.33	45.94 ± 3.91	0.5536
ICW (L)	31.91 ± 3.20	32.13 ± 3.07	0.5895
ECW (L)	13.70 ± 1.99	13.80 ± 1.78	0.6898
ECW/ICW	0.43 ± 0.06	0.43 ± 0.06	0.9435
FFM (Kg)	49.41 ± 4.59	49.99 ± 4.48	0.3439
FM (Kg)	23.95 ± 4.05	23.96 ± 3.62	0.9886
FFM/FM	2.12 ± 0.41	2.13 ± 0.38	0.8154

TBW: total body water; ICW: intracellular water; ECW: extracellular water; ECW/ICW: ratio between extracellular and intracellular water; FFM: fat-free mass; FM: fat mass.
Data are reported as mean ± DS.

Table 3. OGTT glucose values and the incidence of gestational diabetes.

	Myo-inositol ($n = 110$)	Placebo ($n = 113$)	p Value
Glycaemia T0 (mg/dl)	84.13 ± 12.94	86.61 ± 23.89	0.3374
Glycaemia T 60′ (mg/dl)	144.09 ± 21.10	148.01 ± 27.42	0.2338
Glycaemia T 120′ (mg/dl)	115.08 ± 19.21	120.71 ± 25.80	0.0666
GDM rate	9 (8.2)	24 (21.2)	0.006
Weight gain at OGTT (kg)	8.33 ± 2.47	9.31 ± 2.66	0.0070

Data are reported as mean ± SD and as frequencies (percentages).

Table 4. Differences between lipid panel values at each time (from gestational period to post-gestational period).

	Variable	Myo-inositol (n = 110)	Placebo (n = 113)	*p* Value
12th/13th week (T0)	HDL	49.64 ± 6.98	50.56 ± 6.70	0.3157
	LDL	93.64 ± 26.73	92.73 ± 32.30	0.818
	Total cholesterol	163.03 ± 26.22	162.74 ± 32.78	0.9432
	Triglycerides	98.74 ± 29.81	97.29 ± 38.40	0.7544
26th/27th week (T1)	HDL	48.15 ± 6.12	48.04 ± 6.02	0.8922
	LDL	114.97 ± 31.09	117.90 ± 35.99	0.5165
	Total cholesterol	192.46 ± 31.17	195.80 ± 35.43	0.457
	Triglycerides	146.68 ± 33.12	149.25 ± 34.40	0.5711
31st/32nd week (T2)	HDL	46.03 ± 5.54	45.83 ± 4.82	0.7788
	LDL	129.03 ± 27.15	133.70 ± 27.01	0.1992
	Total cholesterol	210.15 ± 23.58	215.27 ± 24.76	0.1154
	Triglycerides	175.43 ± 47.71	178.65 ± 49.99	0.6225
3 weeks after delivery (T3)	HDL	48.90 ± 4.95	49.30 ± 4.11	0.5105
	LDL	110.71 ± 30.57	116.35 ± 32.02	0.1801
	Total cholesterol	190.39 ± 29.83	196.51 ± 32.39	0.1438
	Triglycerides	153.89 ± 41.87	154.30 ± 43.44	0.9429

Data are presented as mean ± DS and expressed as mg/dl.

Table 5. Differences between fluid body compartments at each time (from gestational period to post-gestational period).

	Variable	Myo-inositol (*n* = 110)	Placebo (*n* = 113)	*p* Value
12th/13th week (T0)	TBW	45.61 ± 4.33	45.94 ± 3.91	0.5536
	ECW	13.70 ± 1.99	13.80 ± 1.78	0.6898
	ICW	31.91 ± 3.20	32.13 ± 3.07	0.5895
26th/27th week (T1)	TBW	49.34 ± 4.60	50.25 ± 4.07	0.1176
	ECW	14.93 ± 2.20	15.55 ± 2.17	0.0352
	ICW	34.41 ± 3.34	34.70 ± 3.12	0.5006
31st/32nd week (T2)	TBW	51.30 ± 4.65	53.82 ± 4.13	<0.0001
	ECW	15.61 ± 2.28	16.74 ± 2.35	0.0003
	ICW	35.70 ± 3.32	37.07 ± 3.16	0.0017
3 weeks after delivery (T3)	TBW	46.66 ± 4.54	49.83 ± 3.94	<0.0001
	ECW	14.08 ± 2.12	15.12 ± 2.12	0.0003
	ICW	32.58 ± 3.22	34.72 ± 3.09	<0.0001

TBW: total body water; ICW: intracellular water; ECW: extracellular water. Data are reported as mean ± DS and expressed as litres.

second primary outcome of our study, in each follow-up considered. Data pointed to a significant difference between myo-inositol and placebo group for ECW on 26th/27th week, 31st/32nd week, and three weeks after delivery. TBW and ICW were significantly different only at 31st/32nd week and three weeks after delivery.

The mean values trend of fluid body compartments (TBW, ECW, and ICW) in the myo-inositol group and placebo group at each time is also expressed in Figure 2.

Restricting the analysis only to gestational period trend (from 12th/13th week to 31st/32nd week), we detected a significant increment of ECW in placebo group compared to myo-inositol one (beta value = 1.04; p-value < 0.0001). Similar results were found for ICW and TBW (beta value = 1.15; p-value < 0.0001 and beta value = 2.19; p-value < 0.0001, respectively).

At three weeks after delivery, there was a significant reduction in the mean values of TBW, ECW and ICW compared to the third-trimester follow-up (31st/32nd week), both in the myo-inositol group and in the placebo one (p-value < 0.0001 for all measures). However, comparing the mean difference of TBW, ECW and ICW between 31st/32nd week and 3 weeks after delivery in the myo-inositol group versus the placebo group, only TBW and ICW were statistically different (p-value = 0.003 and p-value < 0.0001, respectively). Also, the global incidence of pregnancy-induced hypertension (PIH), was significantly lower in the myo-inositol group (n = 8, 7.3%) than in the placebo group (n = 24, 21.2%) (p-value = 0.0434).

Two cases of preeclampsia were recorded, both in the placebo group and diagnosed at 31st/32nd week, while no cases of eclampsia occurred in the two groups. The percentages of gestational age at delivery, birth weight, caesarean sections in emergency, macrosomia, shoulder dystocia, neonatal hypoglycaemia, and babies transferred to the Neonatal Intensive Care Unit were similar in both groups.

Discussion

GDM is widespread throughout the world, and its incidence is expected to increase further in the next years, thus representing a real epidemic. As extensively highlighted in the first chapter, GDM is associated with a higher risk of foetal morbidity and mortality, both during the pregnancy and in the postnatal period (Davey 2005). Besides, women affected by GDM and their offspring present an increased risk of developing diabetes mellitus and metabolic dysfunction in the course of life (Shah et al. 2008).

Therefore, the implementation of prevention strategies for this disorder is undoubtedly to be preferred compared to its treatment. Currently, the prevention

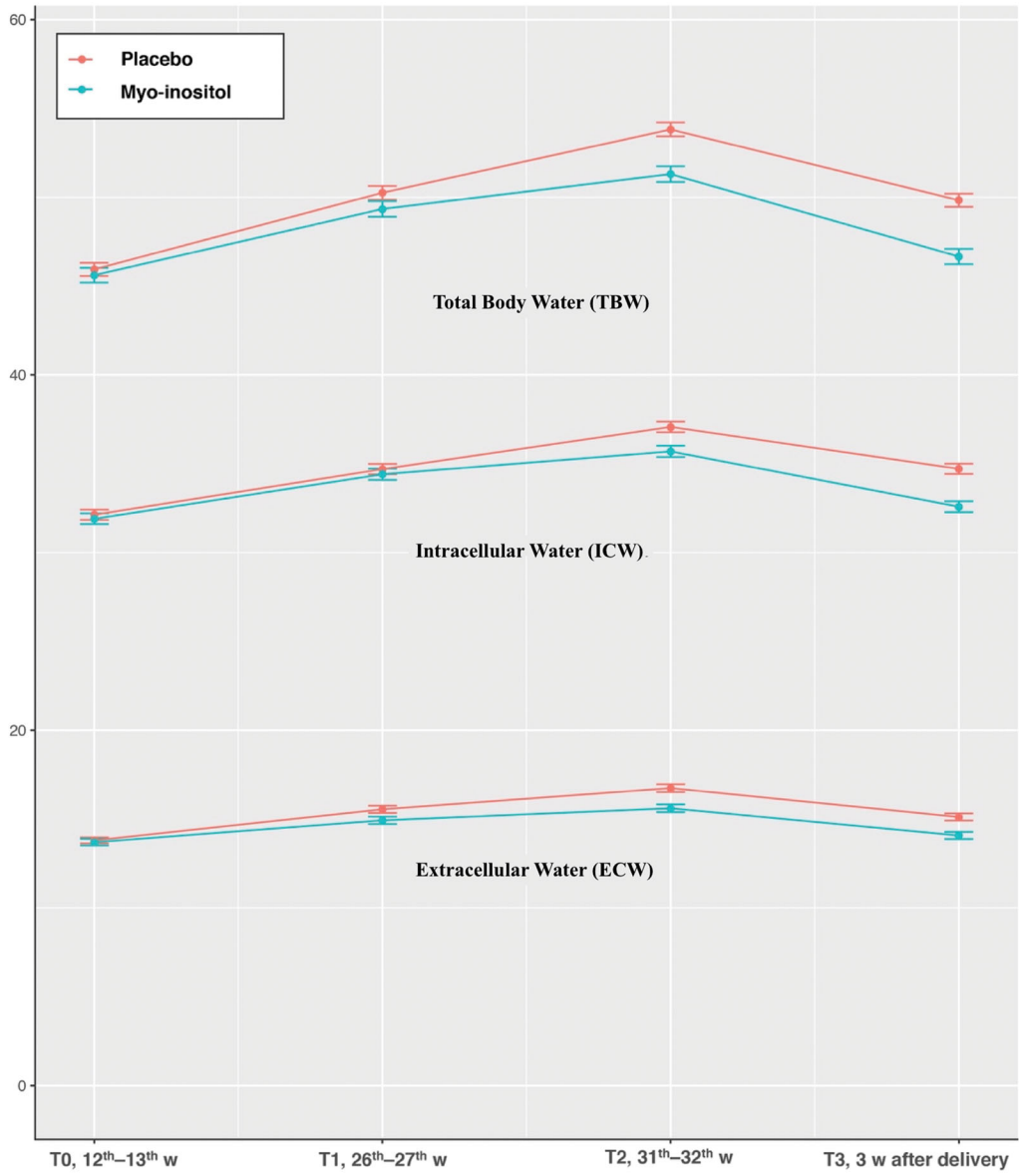

Figure 2. Mean values trend of body fluid compartments at each time (from gestational period to post-gestational period).

of GDM is based mainly on lifestyle interventions such as diet and physical activity (Bain et al. 2015).

Some supplements can represent valid options; in particular, myo-inositol has proved to be an insulin sensitiser substance able to improve glucose homeostasis, as already described in previous studies about the topic (Facchinetti et al. 2014).

The results of our study show a reduction of the incidence of GDM in overweight women who undergo myo-inositol supplementation since the early stages of pregnancy, confirming the data of previous studies that have already highlighted the positive action of this molecule (D'Anna et al. 2013, 2015; Santamaria et al. 2016).

It has been widely demonstrated that maternal high pre-pregnancy body weight and BMI are associated with worse pregnancy outcomes, with particular reference to the development of GDM, hypertensive disorders of pregnancy, and other adverse foetal outcomes. Glucose and lipid metabolism, probably already altered in overweight women, is further compromised during pregnancy, and this alteration could explain the association with more adverse pregnancy outcomes (Pintaudi et al. 2014; Zhang et al. 2014).

In order to confirm this, it has been underlined that body fat is closely related to insulin resistance (Gur et al. 2014) and beta-cell function (Kahn et al. 2001) in pregnant women. However, it is essential to underline that body weight (BW) and BMI do not always allow us to estimate body composition, mainly body fat, accurately.

In light of this, BIA has progressively established itself as one of the most popular methods for evaluation of body composition. It is a benign and non-invasive procedure and allows to evaluate the distribution of the various body compartments during pregnancy, including FM, FFM, TBW, ECW, and ICW (Larciprete et al. 2003).

According to the results of several studies about this topic, FM does not change significantly in the first trimester of pregnancy; nevertheless, an increase in BW and FM values during the second-trimester is positively associated with a higher risk to develop GDM (Hedderson et al. 2008; Fattah et al. 2010; Sommer et al. 2014).

Indeed, because of the effects of subcutaneous fat, leptin (Yilmaz et al. 2010) and TNFα (Kirwan et al. 2002) secretion can increase while insulin sensitivity decreases; furthermore, insulin resistance can increase due to visceral fat (Gur et al. 2014). As a result, significant increases in maternal FM during early pregnancy could strongly influence the subsequent insulin resistance (Hedderson et al. 2010).

According to these data, also our study shows a significant positive correlation between the development of GDM and higher FM, higher pre-pregnancy BMI, and weeks of gestation.

During pregnancy, resting energy expenditure (REE) depends primarily on FFM. FFM in pregnancy includes expanded plasma, foetal, and uterine tissues (requiring high energy) and skeletal muscle mass (requiring moderate energy); changes in FFM are one of the leading causes of variations in energy expenditure. Indeed, total energy expenditure, basal metabolic rate, sleeping metabolic rate (SMR), and minimal SMR in pregnancy are strongly predicted by FFM values. Higher FFM is related to an increased glucose demand and to endogenous glucose output, which can help in glycemic control. These data may partly explain the finding that FFM was negatively associated with GDM in our clinical trial.

Another critical aspect that is highlighted by the bioimpedance analysis during pregnancy is the reorganisation of the water compartments during the different weeks of gestation. Two different water compartments can be distinguished in the human body: ECW and ICW. ECW is the result of interstitial fluid and plasma volume, and its value quickly increases up to 10% above baseline by the seventh week up to stabilise at about 45–50% during the 32nd week of gestation. ICW is strictly associated to the changes in the maternal body during pregnancy, such as increases in mammary and uterine tissues, that take place in preparation for labour, delivery, and the puerperium (Cho et al. 2011).

Obese and overweight women present a higher ECW/ICW ratio than normal-weight ones because the fluid in adipose tissue is mainly distributed at the extracellular level (Wang and Pierson 1976).

These data can explain the results of our study, according to which a higher ECW is associated with a higher risk of GDM. Hence, we hypothesised that a higher FM is a probable risk factor for the development of GDM also in these subjects.

It has also been underlined that the relationship between ECW increase and hypertension depends on the development of hypervolemia, increased cardiac output, and the subsequent rise in the total peripheral resistance reducing volume expansion and normalising systemic flow while maintaining a high systolic and diastolic pressure (Tarazi 1976). These events have not been demonstrated in all forms of hypertension but only in some human and experimental ones; despite this, however, it is possible to consider them as one of the causes of obesity-induced hypertension (Kotsis et al. 2010).

In agreement with these observations, our study demonstrated the existence of a significant association between the risk of PIH and a higher ECW, in a model adjusted for FM, treatment groups, and pregnancy weeks.

Conclusions

The results of the present study demonstrated a significant increase in TBW, ECW and ICW values in the placebo group compared to the myo-inositol group. We have also recorded a significant reduction of the overall incidence of pregnancy-induced hypertension (PIH) in the myo-inositol group compared with the placebo group

However, despite the innovative nature of this study, it has some limitations. First of all, this trial used a protocol treatment analysis. Further studies using intention-to-treat analyses are recommended to avoid biases in the results. Secondly, we hypothesised that the results of the analysis of the maternal body fluid composition through BIA could be influenced by the presence of amniotic fluid and the foetus and that this could be a possible limit of our study. The differences between the two groups could have been better explained through the data related to serum osmolarity and albumin concentrations that were not detected in our clinical trial. Furthermore, the use of drugs in patients who developed gestational hypertension could be considered as a possible confounder. Finally, the open-label placebo may represent a limitation of the

study, although the literature on this point has shown that subjects receiving an open-label placebo can experiment benefits compared to those who are aware of taking a placebo. For this reason, further studies with a double-bling design would be advisable to confirm the results of this study.

Despite these limitations, it has been demonstrated that the BIA may be considered a useful tool for a more appropriate antihypertensive treatment. Moreover, the BIA may help evaluate the effectiveness of pharmacological antihypertensive treatment as it provides an estimate of volume restoration of the different body compartments.

In conclusion, literature data about changes in body compartments during pregnancy are still conflicting. For this reason, further studies are needed to better clarify this topic, especially in patients with GDM and hypertensive complications.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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