Clinical Trial

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Can trans resveratrol plus d-chiro-inositol and myo-inositol improve maternal metabolic profile in overweight pregnant patients?

A. Malvasi[1], I. Kosmas[2], O.A. Mynbaev[3], R. Sparic[4], S. Gustapane[5], M. Guido[6], A. Tinelli[7]

[1]Department of Obstetric & Gynecology, Santa Maria Hospital, GVM Care & Research, Bari, Italy; Laboratory of Human Anatomy, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia; [2]Department of Obstetrics and Gynecology, University of Ioannina, Medical School, Greece; Laboratory of Human Anatomy, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia; [3]Laboratory of Human Anatomy, Moscow Institute of Physics and Technology (State University), Dolgoprudny, Moscow Region, Russia; Peoples' Friendship University of Russia, Moscow, Russia; Moscow State University of Medicine and Dentistry, Moscow, Russia; [4]School of Medicine, University of Belgrade, Belgrade, Serbia, Clinic for Gynecology and Obstetrics, Clinical Center of Serbia, Belgrade, Serbia; [5]Department of Obstetric and Gynecology, Salus Hospital, Brindisi, Italy; [6]Laboratory of Hygiene, Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy; [7]Department of Obstetrics and Gynecology, Division of Experimental Endoscopic Surgery, Imaging, Technology and Minimally Invasive Therapy; Laboratory of Human Anatomy, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia; Department of Obstetrics and Gynecology. Vito Fazzi Hospital, Lecce, Italy

Abstract

Objective. To investigate the effect of trans-resveratrol from Polygonum cuspidatum/magnesium hydroxide complex, trademark Revifast®, plus D-chiro-inositol (DCI) and Myo-inositol (MI) during spontaneous pregnancies in overweight patients in a pilot study.

Study design. A one-year, prospective, randomized, double-blinded, placebo-controlled single center clinical study was carried out on overweight pregnant women. 110 patients were randomized in 3 groups to receive: Revifast® with DCI/MI (group I), DCI/MI alone (group II) or control group (group III) for 30 and 60 days. The main outcomes were to explore the lipid profile (total cholesterol, LDL, HDL, TG) and glucose levels, after 30 and 60 days of therapy.

Results. No difference in systolic and diastolic parameters among 3 groups during study. All blood chemistry parameters improved compared to placebo at 30 days already, but significantly to 60 days, respect placebo. By comparing the two treatment groups, group I demonstrates significantly improved lipid and glucose parameters than group II, which are at 30 to 60 days of treatment.

Conclusion. The supplementation of Trans-resveratrol, Revifast® in addition to DCI/MI in overweight pregnant woman with an elevated fasting glucose improves glucose levels, Total Cholesterol, LDL and TG. ***Clin Ter 2017; 168(4):e240-247. doi: 10.7417/CT.2017.2013***

Key words: *Trans-resveratrol, Inositol, Myo-inositol, D-chiro-inositol, pregnancy, metabolic syndrome, insulin resistance, hyperglycaemia, gestational diabetes*

Introduction

Maternal metabolic profile in pregnancy is widely involved in developing of gestational diabetes mellitus (GDM), defined as "glucose intolerance with onset or first recognition during pregnancy" (1-2). GDM is usually detected using an oral glucose tolerance test (OGTT) between 24 to 28 weeks of gestation, but guidelines and the diagnostic criteria vary among countries and between major societies worldwide (3-11), making estimates of prevalence difficult.

GDM is a significant problem both the immediate and long-term outcome for the mother and baby as demonstrated by HAPO study (12). Complications of GDM, even at the milder form, include fetal macrosomia, neonatal adiposity, congenital malformation, pre-eclampsia, and cesarean section (13). All these can be reduced by early diagnosis and treatment of GDM (14-16). HAPO study demonstrated a correlation between early pregnancy fasting glucose levels and earlier onset of GDM (12). The ongoing epidemic of obesity (main risk factor related to decreased insulin sensitivity) has led to more cases of type two diabetes. In addition, the number of pregnant women with undiagnosed type 2 diabetes has increased (13).

Currently, treatment includes lifestyle modification and pharmacological therapy in order to control blood glucose and cholesterol levels (14-16). One such emerging potential

Abbreviation

GDM: Gestational diabetes mellitus; MI: Myo-inositol; DCI: D-chiro-inositol; DCI/MI: D-chiro-inositol and Myo-inositol; OGTT: oral glucose tolerance test; PCOS: polycystic ovary syndrome; CVR: cardiovascular disease; IR: insulin resistance; MS: Metabolic Syndrome; P-IPG: phosphoglycan P-type

Correspondence: Prof .Antonio Malvasi, Department of Obstetric & Gynecology, Santa Maria Hospital, GVM Care & Research, Bari, Italy; Laboratory of Human Anatomy, Department of Applied Mathematics, Moscow Institute of Physics and Technology (State University), Moscow Region, Russia. Email: antoniomalvasi@gmail.com

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intervention is inositol present in two form: Myo-inositol and D-chiro-inositol (DCI) showed insulin-mimetic properties efficient in lowering post-prandial blood glucose (17). Myo-inositol which is an isomer of inositol and is a component of inositol-phosphoglycan, a second messenger for insulin action. Inositol is present in many foods, particularly fresh fruits and vegetables, beans, grains, and nuts. The potential benefits of a dietary supplement of Myo-inositol have been studied in the last years (18-20).

Recent studies have demonstrated that resveratrol (*trans*-3,5,4′-trihydroxystilbene), a grape antioxidant found in red grapes and blueberries, lowers maternal blood sugar, improves maternal lipid profile (21) and prevents developmental delays in embryos of rat diabetic dams. Because of these results, resveratrol could be a potential therapeutic agent for the prevention of embryonic malformations including NTDs (22). Thus, resveratrol was successfully evaluated in prevention of diabetic embryopathy (23); moreover, administration of resveratrol to diabetic rats results in a significant decrease in blood-glucose concentrations, glycosylated hemoglobin, blood urea and other blood compounds that are usually elevated in type II diabetes and cause damage to body organs (23).

Resveratrol action has been linked to the activation of a histone deacetylase Sirtuin 1 (Sirt1) and notably, when Sirt1 is activated by resveratrol, diabetes is improved (24).

Resveratrol use in humans has no pronounced toxicity, and orally administered *trans*-resveratrol is well absorbed. Orally ingested resveratrol is both rapidly metabolized and excreted, accounting for its low bioavailability. However, a few studies show that the bioavailability of resveratrol can be enhanced by using more potent trans-resveratrol, Revifast®. Authors decided to test, in a preliminary study, the metabolic effect of Revifast® combined or not with myo-inositol e D-chiro-inositol in pregnant overweight women, evaluating the metabolic effects in second trimester of pregnancy.

Research design and methods

From January to December 2016, 70 consecutive outpatient pregnants have been enrolled for the study, settled in private outpatient clinic. The study design was a prospective, randomized, double blinded, placebo-controlled clinical trial. The patients, all with single pregnancy, received all information concerning the study protocol and outcomes. All patients provided a written informed consent prior to enrollment. All procedures used in the present study were in accordance with guidelines of the Helsinki Declaration on human experimentation. All women consented to publish their data, without possibility to be recognized.

The inclusion criteria were: pregnant aged from 25 to 40 years, gestational age at enrollment between the 24th and 28th weeks' gestation, with a pregnancy body mass index (BMI), in first trimester, between 25-30 (kg/m2).

Exclusion criteria were settled before enrolling, as followings: diabetes mellitus, cardiovascular disease, chronic hypertension, autoimmune disease, thyroid disease, ART.

The study protocol was as followings: at first visit, a careful anamnesis, mean systolic and diastolic blood pressure, age, parity and BMI have been recorded. The following blood parameters were tested: total cholesterol, LDL, HDL, triglycerides and blood glucose. All patients tested in two clinical laboratories with national accreditation regarding the quality of analytical data.

Patients were randomly assigned to receive either Revifast® plus Myoinositol - D-chiro-inositol (DCI/MI), as Group I, either DCI/MI alone, as Group II, or placebo, as Group III, with a random number table and an assignation 1:1:1 and randomization list was kept by an outpatients nurse, not involved in the study. Group I of 35 women was orally treated by Kirocomplex (S&R Farmaceutici S.p.A., Bastia Umbra, Perugia, Italy), group II was orally by Inofert Combi (Italfarmaco S.p.A., Milano, Italy) and group III by placebo (35 women). The Kirocomplex had 80 mg of Revifast®, 200 mg of myo-inositol, 500 mg D-chiro-inositol. The Inofert Combi had 138 mg of myo-inositol, 550 mg D-chiro-inositol. All parameters have been collected and compared, after 30 and 60 days, in all three groups at the same gestational age. All patients have been assigned to the randomization list and given dietary advice according to American Diabetes Association recommendations.

Statistical analysis

The method of allocation in two groups was controlled by an independent statistician who assigned numbered patients to groups. The statistician used sealed numbered containers and clinicians received the container in the ambulatory. To avoid a confounding factor, there was a consensus among clinicians involved in this study that, when they received a container, they would not abandon the MDFM administration determined by the statistician in favor of other supplements or medications. All analyses were performed using SPSS 18.0 (Chicago, USA). Continuous variables were expressed as mean ± standard deviation (SD). The homogeneity of variances was evaluated using the Levene test. Finally, an independent statistician elaborated the data with statistical comparison by ANOVA analysis on Kruskal-Wallis test and t-Student test. $p < 0.05$ was considered statistically significant.

Results

During the enrollment of 110 pregnant women, six patients were excluded: three left after the first visit, three did not meet inclusion criteria. The remaining 104 women have been allocated in the three groups as follows: 35 in the group I, 34 in the group II and 35 in group III. The number of women completed the follow-up period was 35 (group I), 34 (group II), 35 (group III) respectively. None of the women reported an adverse reaction to therapy. All data on patients are reported on Figure 1.

Baseline maternal characteristics, for Age, parity and BMI, were similar in the three groups (Table 1) and there were no differences between the three groups for systolic and diastolic pressure (Table 2). The difference among treated and placebo groups was significant for group I and II, in reduction of total cholesterol, LDLD, HDL, triglycerides, fasting glucose level. Data analysis showed a significant

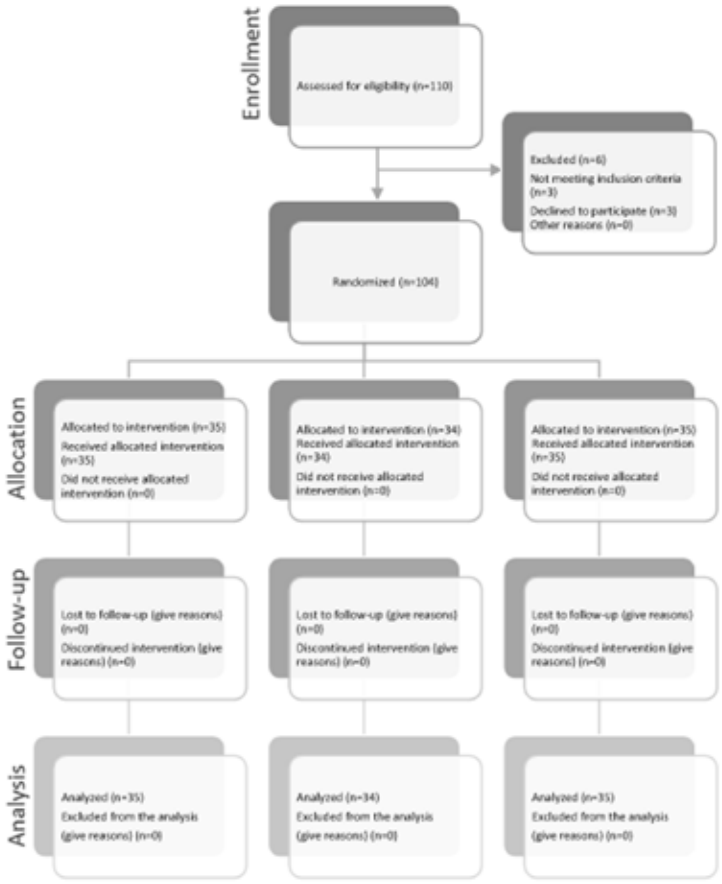

Fig. 1. A Flow-diagram reporting all data on the patients' enrollment, allocation, follow up and analysis.

Table 1. Baseline characteristics of the 109 women: Revifast® with DCI/MI (group I), DCI/MI alone (group II) or placebo (group III).

Characteristic	Group I 35 patients	Group II 34 patients	Group III 35 patients	P
Age	31.88 ± 4.42	32.35 ±4.62	32.31 ± 5.99	0,913
Parity	1.085±0.98	1.11±1.007	1.028± 0,785	0,921
BMI	26.75±1.16	27.43±1.28	26.82± 1,41	0,0618

*Analysis of Variance-One Way Anova

values reduction of lipid and glucose parameters already after 30 days, but especially after 60 days, either in those patients who received Revifast® plus DCI/MI, as Group I, or in patients who received DCI/MI alone, as Group II (Table 2).

Anyhow, the screening for GDM at 24–28 weeks' gestation, using a 75-g 2-h OGTT was negative for all patients. Finally, comparing only both treated groups, at 0, 30 and 60 days, statistical evaluation showed a significant improvement of lipid and glucose profiles in group I compared to group II, while no difference was noticed for systolic and diastolic profile between groups (Table 3).

For triglycerides, in 30 days significant differences in between groups have been presented (1 vs 2 P=0,014 and 2 vs 3 p=0,004). Always for triglycerides, in 60 days significant differences in between groups have been presented (1 vs 2 P=0,025 and 2 vs 3 p=0,000). For cholesterol, in 30 days significant differences in between groups have been presented (1 vs 2 P=0,002 and 2 vs 3 p=0,000). Always for cholesterol, in 60 days significant differences in between groups have been presented (1 vs 2 P=0,005 and 2 vs 3 p=0,000). For LDL, in 30 days no significant differences in between groups have been presented (1 vs 2 P=0,097, significant differences between 2 vs 3 p=0,000). Always for LDL, in 60 days no significant differences in between groups have been presented (1 vs 2 P=0,225, significant differences between 2 vs 3 p=0,000). For HDL, in 30 days no significant differences in between groups have been presented (1 vs 2 P=0,657, significant differences between 2 vs 3 p=0,004). Always for HDL, in 60 days no significant differences in between groups have been presented (1 vs 2 P=0,119, significant differences between 2 vs 3 p=0,000). For Glycemia,

Table 2. Treatment characteristic of patient, before treatment, in 30 days and in 60 days of three groups: Revifast® with DCI/MI (group I), DCI/MI alone (group II) or placebo (group III).

Time to treatment	group	n	mean± SD	P
Systolic Pressure				
0 days	1	35	119,64±5,56	
	2	34	118,52±7,58	0.1890
	3	35	121,44±6,70	
30 days	1	35	119,20±5,57	
	2	34	118,54±6,61	0.1120
	3	35	121,39±5,39	
60 days	1	35	117,35±6,90	
	2	34	118,51±5,41	0.0240
	3	35	121,60±7,32	
Diastolic Pressure				
0 days	1	35	76,21±5,48	
	2	34	78,15±6,37	0.0790
	3	35	79,32±5,41	
30 days	1	35	77,30±7,12	
	2	34	75,28±6,14	0.5110
	3	35	76,27±8,22	
60 days	1	35	77,56±7,26	
	2	34	75,68±5.41	0.2760
	3	35	78,11±6,77	
Cholesterol (total)				
0 days	1	35	225,18±9,80	
	2	34	228,22±10,15	0.4800
	3	35	226,30±11,43	
30 days	1	35	210,52±7,52	
	2	34	216,70±8,14	0.0001
	3	35	224,41±9,24	
60 days	1	35	202,50±8,95	
	2	34	209,65±11,38	0.0001
	3	35	240,19±10,12	
LDL				
0 days	1	35	159,43±9,89	
	2	34	162,18±10,75	0.5600
	3	35	161,34±11,87	
30 days	1	35	140,57±11,29	
	2	34	145,18±11,48	0.0001
	3	35	158,57±10,10	

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60 days	1	35	136,51±11,29	0.0001
	2	34	139,64±9,88	
	3	35	163,71±11,46	
HDL				
0 days	1	35	76,69±7,82	0.359
	2	34	74,20±7,95	
	3	35	75,93±6,18	
30 days	1	35	67,60±8,84	0.0010
	2	34	68,59±9,57	
	3	35	74,93±7,85	
60 days	1	35	58,25±7,46	0.0001
	2	34	61,47±9,41	
	3	35	70,36±8,35	
Triglycerides				
0 days	1	35	175,71±6,29	0.1900
	2	34	178,47±7,17	
	3	35	176,25±6,32	
30 days	1	35	164,29±8,62	0.0001
	2	34	169,18±7,44	
	3	35	175,43±9,60	
60 days	1	35	156,21±7,59	0.0001
	2	34	160,55±8,12	
	3	35	177,58±8,27	
Glycaemia				
0 days	1	35	80,22±8,13	0.8730
	2	34	81,14±7,39	
	3	35	80,41±7,61	
30 days	1	35	71,27±8,28	0.0001
	2	34	73,33±7,60	
	3	35	81,42±10,13	
60 days	1	35	68,18±7,24	0.0001
	2	34	69,33±8,35	
	3	35	83,36±8,51	

in 30 days no significant differences in between groups have been presented (1 vs 2 P=0,286, significant differences between 2 vs 3 (p=0,000). Always for Glycemia, in 60 days no significant differences in between groups have been presented (1 vs 2 P=0,543, significant differences between 2 vs 3 (p=0,000).

In our previous prospective randomized controlled trial (25),significant differences has been found in total cholesterol, TG, glucose and mean pressure in 30 days of administration and in Total Cholesterol, LDL, HDL and TG for 60 days of administration. We examined two groups at that time. Now we added a control group and we found that less than 10 patients in each group, are required to achieve these significant differences and to achieve an 80% power with a=0.05.

Discussion

The present randomized controlled clinical trial was designed to test the hypothesis that the use of trans-resveratrol/magnesium complex (Revifast®) , in combination with Myo-inositol and D-chiro-inositol in late pregnancy, reduces the risk of developing GDM and improves the lipid profile and glucose blood levels after 60 days.

In fact, the screening for GDM at 24–28 weeks' gestation, using a 75-g 2-h OGTT was negative for all patients, but significant difference has been found in total cholesterol, HDL, LDL, triglycerides and glucose levels after 30 days of treatment by Revifast®, even better after 60 days. Thus, trans resveratrol supplementation to DCI/MI showed positive biological effects on metabolic pathways in pregnants. A study showed that maternal resveratrol administration in pregnant mice recovered metabolic activity of offspring brown

Table 3. Comparison of parameters in two treated groups, Revifast® with DCI/MI (group I), DCI/MI alone (group II), at 0 & 30 and 0 &60 days of treatment.

Characteristic Group I & II at 0 days	**Group I & II Comparison 0 - 30 days**	**P**	**Group I & II Comparison 0 - 60 days**	**P**
Systolic Pressure 119,64±5,56 118,52±7,58	119,20±5,57 118,54±6,61	0.8600	117,35±6,90 118,51±5,41	0.5290
Diastolic Pressure 76,21±5,48 78,15±6,37	Diastolic Pressure 77,30±7,12 75,28±6,14	0.2610	Diastolic Pressure 77,56±7,26 75,68±5.41	0.3180
Cholesterol (total) 225,18±9,80 228,22±10,15	Chol tot 210,52±7,52 216,70±8,14	0.0001	Chol tot 202,50±8,95 209,65±11,38	0.0001
LDL 159,43±9,89 162,18±10,75	LDL 140,57±11,29 145,18±11,48	0.0001	LDL 136,51±11,29 139,64±9,88	0.0001
HDL 76,69±7,82 74,20±7,95	HDL 67,60±8,84 68,59±9,57	0.0001	HDL 58,25±7,46 61,47±9,41	0.0001
Triglycerides 175,71±6,29 178,47±7,17	Triglycerides 164,29±8,62 169,18±7,44	0.0001	Triglycerides 156,21±7,59 160,55±8,12	0.0001
Glucose (blood) 80,22±8,13 81,14±7,39	Glucose (blood) 71,27±8,28 73,33±7,60	0.0001	Glucose (blood) 68,18±7,24 69,33±8,35	0.0001

adipose tissue, promoting beige adipocyte development in offspring white adipose tissue and protecting offspring against high-fat diet-induced obesity (26).

Perinatal maternal trans resveratrol supplementation mitigated the development of hypertension and caused persistent alterations in vascular responsiveness in spontaneously hypertensive rats (27).

Authors investigated effect of trans resveratrol supplementation on the pregnant db/+ GDM mouse model, and the underlying molecular mechanism. Resveratrol greatly improved glucose metabolism, insulin tolerance and reproductive outcome of the pregnant db/+ females. Moreover, they found that resveratrol relieved GDM symptoms through enhancing AMPK activation, which in turn reduced production and activity of glucose-6-phosphatase in both pregnant db/+ females and their offspring (28).

Currently, GMD treatment resides in diet, oral hypoglycemic agents or insulin, but the appearance of supplements consisting of DCI and MI arousing interest. Costantino et al (29) showed that the DCI supplement had a role in the regulation of glucose metabolism improving insulin sensitivity and reducing the onset of gestational diabetes in pregnant women at risk, decreasing the weight gain and nocturnal hypoglycemia responsible for the attacks of hunger at night.

From the other side, GDM may be an expression of early metabolic syndrome. It is unknown whether weight and/or glucose parameters assessed at GDM pregnancies predict the risk of metabolic syndrome at the early postpartum period. Barquiel et al affirm that this risk can be easily identified by assessing pre-pregnancy BMI and antenatal fasting glycaemia in the first pregnancy visit (30).

The diagnosis of a Metabolic Syndrome (MS) that takes place before or during pregnancy is important to change the lifestyle and diet. It is recommended that the patient have to follow a proper diet scheme as suggested by several studies (31).

Hans and Crowether considered that gestational diabetes mellitus (GDM) affects a significant number of women each year and is associated with a wide range of adverse outcomes for women and their babies. Dietary counselling is the main strategy in managing GDM, but it remains unclear which dietary therapy is the best. They assessed the effects of different types of dietary advice for women with GDM on pregnancy outcomes (32).

Luoto et al examined whether GDM or newborns' high birth weight can be prevented by lifestyle counseling in pregnant women at high risk of GDM, changing physical activity and the decreasing the intake of total fatty acids, saccharose and increasing fiber intake; this intervention was effective in controlling birth weight of the newborns, but failed to have an effect on maternal GDM (33).

In a recent study, Matarrelli et al. concluded that MI supplementation in pregnancy reduced the incidence of GDM in women at high risk of this disorder. The reduction in incidence of GDM in the treatment arm was followed by improved outcomes. The incidence of GDM in mid-pregnancy was significantly reduced (p=0.001) in women who received MI compared to placebo group (relative risk 0.127). Women who received MI also required less insulin therapy, delivered at a later gestational age, had significantly smaller babies with fewer episodes of neonatal hypoglycaemia (19).

Also in preeclampsia, there is exacerbation of physiological changes associated with pregnancy such as insulin resistance, altered immune responses and inflammatory pathway activation. These exaggerated responses seen in preeclampsia are reminiscent of metabolic syndrome, and are evident in gestational diabetes mellitus. The link between these phenomena is not clear but novel findings

providing some insight have been reported recently. Inositol phosphoglycan P-type (P-IPG) in preeclampsia has been extensively investigated and increased production has been demonstrated. This molecule acts as a second messenger of insulin, enhances the metabolic effects of insulin and is associated with insulin resistance (34).

An increase in urinary release of P-IPG during pregnancy may herald the onset of preeclampsia. Urinary levels of P-IPG, were assessed in insulin resistant states during pregnancy such as gestational diabetes mellitus with a higher P-IPG urinary excretion with a positive association with poor glycemic control (35).

Pathophysiological basis of the effectiveness of this treatment is because several inositol isomers and in particular MI and DCI, showed insulin-mimetic properties and efficiency in lowering post-prandial blood glucose. In addition, abnormalities in inositol metabolism are associated with insulin resistance and with long-term microvascular complications of diabetes, supporting a role of inositol or its derivatives in glucose metabolism (13).

MI is one of the most relevant isomeric forms of inositol present in nature and can be synthesized by the body in the follicular microenvironment; various natural forms of Inositol also exist, among which the most studied is the DCI, which is not synthesized from precursors in human body but obtained from epimerization of MI (20).

The activity of the epimerase is reduced in type 2 diabetes mellitus and in polycystic ovary syndrome (PCOS), one of the most frequent causes of endocrine disruption and infertility by chronic anovulation in women of childbearing age (29).

About limitations of such investigations, we have to report that, although significant differences have been obtained in previous studies, we aimed to test whether these results exist in a sufficient sample size, and this is true. Obviously, a study with a much larger sample size should be conducted and special group of patients that benefit more should be identified. Such a study currently is under design.

Conclusions

The addition of trans-resveratrol, Revifast®, to DCI/MI was most effective than DCI/MI alone in reducing Total Cholesterol, HDL, LDL, Triglycerides and glucose blood levels after 30 days of treatment, even mostly to 60 days. This approach could be considered useful to the patients with risk factors for metabolic syndrome that may evolve also to gestational diabetes. Our results suggest that the administration of Revifast® to DCI and MI will lead to a significant reduction if taken for 30 days at least, preferably for 60 days, basing on our preliminary results. Further studies would be desirable to clarify the mechanism of action of trans-resveratrol at the cellular level in glucose metabolism during pregnancy, and clinical data must be confirmed with wider cohort of patients.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this article.

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