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Myo-inositol, D-chiro-inositol, folic acid and manganese in second trimester of pregnancy: a preliminary investigation

A. MALVASI[1], F. CASCIARO[2], M.M. MINERVINI[2], I. KOSMAS[3], O.A. MYNBAEV[4], E. PACELLA[5], V. MONTI CONDESNITT[6], A. CREANZA[1], G.C. DI RENZO[7], A. TINELLI[8]

[1]Department of Obstetrics and Gynecology, Santa Maria Hospital, Bari, Italy
[2]Department of Human Physiology and Pharmacology, University of Bari, Italy
[3]Department of Obstetrics and Gynecology, Xatzikosta General Hospital, Ioannina, Greece
[4]Moscow Institute of Physics and Technology (State University), Moscow State University of Medicine and Dentistry, Peoples' Friendship University of Russia, Moscow, Russia
[5]Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy
[6]Associazione Culturale Pediatri (ACP), ASL Taranto 1, Taranto, Italy
[7]Department of Obstetrics and Gynecology, University of Perugia, Perugia, Italy
[8]Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Abstract. – DESIGN AND PURPOSE: The supplemental administration of myo-inositol, D-chiro-inositol, folic acid and manganese (MDFM) was tested in a prospective, randomized, double-blind, placebo controlled clinical trial, pilot study, to test the hypothesis that its supplemental administration in the second trimester of pregnancy would improve glucose and glycemic parameters and blood pressure.

SUBJECTS AND METHODS: Non-obese uniparous healthy pregnant women between 13th and 24th week of pregnancy were divided into two groups: group I, control group with placebo, and the group II, women in treatment with myo-inositol, D-chiro-inositol, folic acid and manganese.

The main outcome measures were the comparative analysis of the parameters analyzed at time 0, after 30 days and 60 days; secondary outcome measure was the overall analysis of investigated parameters.

RESULTS: 24 women were allocated to receive MDFM and 24 the placebo. The two groups did not significantly differ for demographic, lipidic and glycemic parameter and blood pressure. After 30 days, significantly lower cholesterol (p = 0.0001), significantly lower LDL (p = 0.0013), lower TG (p < 0.0001) and lower glycemia (p = 0.0021) were observed all favoring group II. No significant difference was observed for HDL, diastolic and systolic blood pressure. After 60 days, significant difference was observed for cholesterol (p = 0.0001), LDL (p = 0.0001), HDL (p = 0.0001), TG (p = 0.0001), glycemia (p = 0.0064), all favoring the group treated with MDFM. No significant differences were observed for systolic (p = 0.12) and diastolic blood pressure (p = 0.42). When examining for overall differences between the two groups, a significant difference was observed for examined parameters at time 0 and at time 60; cholesterol (p = 0.0001), LDL (p = 0.0001), HDL (p = 0.047), TG (p = 0.0001) and glycemia (p = 0.019) were reduced in the MDFM group. A significant reduction was also observed in group II for systolic blood pressure after 60 days of intervention (p = 0.0092), but not for diastolic blood pressure (p = 0.29).

CONCLUSIONS: MDFM administration after 30 days in pregnancy improved glycemic and lipidic parameters, with significant gain after 60 days, without affecting diastolic blood pressure levels.

Key Words:
Inositol, Pregnancy, Gestational diabetes, Myo-Inositol, D-chiro Inositol, Obstetric outcomes, PCOS, Hypertension in pregnancy, Pre-eclampsia

Introduction

Inositol or cyclohexane-1,2,3,4,5,6-hexol is a chemical compound discovered in 1936. Some studies consider it as similar to a vitamin nutrient. At the same time, others classify it as part of the B complex with the acronym vitamin B7. The liver and kidneys are involved in Inositol endogenous synthesis. Inositol is contained in several foods, above all in whole grain, cereals, legumes, dried fruit, grain seeds, brewer's yeast, fresh citrus fruit and meat in general. Inositol

Corresponding Author: Antonio Malvasi, MD; e-mail: antoniomalvasi@gmail.com

has two stereoisomers: myo-inositol and D-chiro-inositol. The biological role of both compounds has specific activity in controlling fat and sugar metabolism, and, in particular, it helps to balance cholesterol levels. Scientific evidence has shown that myo-inositol supplement helps to improve ovarian function. Because of these latter specific activities, the synergistic association of myo-inositol and D-chiro-inositol may be useful in preventing and improving the polycystic ovary syndrome (PCOS)[1,2]. Inositol is required for correct nerve and cerebral function as in exerting its neuroprotective activity, it seems to improve nerve conduction[3]. Myo-inositol has sedative and anti-anxiety activity and it also seems to exert effective action in reducing symptoms of pre-menstrual syndrome (PMS)[4]. When contained in dietary supplements, Myo-inositol needs doses from 500 to 2,000 milligrams a day, depending on mode of use and association with other active compounds. According to a recent study, the best pharmaceutical administration form of myo-inositol seems to be the soft gelatin capsules which have shown a better bioavailability thus allowing lower doses of myo-inositol in single capsules[5]. Diets with a decreased level of Inositol show elevation of cholesterol, triglycerides and intra-hepatic lipids, within all tissues. These effects demonstrate the utility of Inositol as a diet supplement as well as its use in supplement form in some patients with PCOS. Recent studies[1,2,5] demonstrate it could be a useful nutritional strategy to prevent and/or treat insulin resistance in type 2 diabetes. To our knowledge, only a few investigations have tested Inositol in pregnancy. The objective of our study was thus to measure biochemical parameters in pregnancy in the second trimester in women who were treated with a supplement of Inositol.

Subjects and Methods

In 2012, from January to December, 65 pregnant women were enrolled in two University-affiliated Hospitals, by a prospective, randomized, double-blind, placebo controlled clinical trial. All procedures used in the present study were in accordance with guidelines of the Helsinki Declaration on human experimentation. The inclusion criteria were: healthy pregnant women, between the 13th and 24th week of gestation, with a body mass index (BMI) between 25-30 (kg/m^2), aged between 30 and 40 years. Exclusion criteria were: diabetes mellitus, cardiovascular disease, chronic hypertension, autoimmune disease, dystyroidism. The study protocol was as follows. At first visit, after a careful anamnesis, clinicians collected mean systolic and diastolic blood pressure and the following demographic characteristics: age, parity and BMI, assigning a number to each patient. The following blood parameters were tested: total cholesterol, LDL, HDL and blood glucose, all tested in two clinical laboratories with national accreditation regarding the quality of analytical data.

The administered drug was a compound of myo-inositol, d-chiro-inositol, folic acid and manganese, called MDFM (commercially named: Dikirogen, Pizeta Pharma S.p.A., Perugia, Italy) and the dosage was as follows: one envelope per day (20 envelops per pocket). Each dose contained: 2000 mg myo-inositol, 400 mg d-chiro-inositol, 400 µg folic acid, and 10 mg manganese. All parameters were collected and compared after 30 and 60 days. Successively, all women were blindly divided into two groups: group I, as control group, group II, women in treatment with MDFM.

Statistical Analysis

The method of allocation in two groups was controlled by an independent statistician who assigned numbered patients to groups, with a randomization ratio of 1:1. 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. 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

Seventeen pregnants enrolled for the study were excluded: 6 did not meet inclusion criteria, 4 refused to participate, 7 left the study spontaneously. No significant differences were observed in patients age ($p = 0.99$ Kruskal-Wallis test), parity ($p = 0.99$ Kruskal-Wallis test) and BMI ($p = 0.59$). No adverse events or side effects were reported in group II.

Baseline clinical characteristics and hematochemical parameters determined in two groups of pregnancy women showed no significant differences (Table I), for cholesterol ($p = 0.0001$), LDL ($p = 0.0001$), HDL ($p = 0.047$), TG ($p = 0.0001$) and glycemia ($p = 0.019$) (Kruskall-Wallis test).

After comparison for blood pressure, no significant difference was observed in systolic pressure ($p = 0.09$), while a significant difference was observed in diastolic pressure ($p = 0.002$).

When comparing the two groups after 30 days for the same parameters, a significantly lower level of cholesterol was observed ($p = 0.0001$), significantly lower LDL ($p = 0.0013$), lower TG ($p < 0.0001$), and lower glycemia ($p = 0.0021$) all favoring group II. No significant difference was observed for HDL, diastolic and systolic blood pressure.

When examining the two groups after 60 days, a significant difference was observed for cholesterol ($p = 0.0001$), LDL ($p = 0.0001$), HDL ($p = 0.0001$), TG ($p = 0.0001$), and glycemia ($p = 0.0064$), all favoring the group treated with MDFM. No significant differences were observed for systolic ($p = 0.12$) and diastolic blood pressure ($p = 0.42$).

All results are detailed in Table II.

When examining for differences between the two groups, significant differences were observed for examined parameters between the first group of values (at time 0) and at the third group (at 60 days).

For cholesterol ($p = 0.0001$), LDL ($p = 0.0001$), HDL ($p = 0.047$), TG ($p = 0.0001$) and glycemia ($p = 0.019$) (Kruskall-Wallis test). A significant difference was also observed in systolic blood pressure after 60 days of intervention ($p = 0.0092$), while this was not observed for the diastolic blood pressure ($p = 0.29$).

All results are detailed in Table III.

Discussion

The results of our study add conviction to the rationale of D-chiro-inositol utilization in pregnancy. It should be targeted to patients with metabolic syndrome or impaired glucose tolerance, pre-diabetes, diabetes, dyslipidemia and perhaps also hyperuricemia. MDFM has positive effects on blood parameters after 30-60 days, as it stabilizes blood glucose and cholesterol levels. The use of Inositol in pregnancy is also preferential in a pre-pregnancy period for pregnant women with high BMI. In these, the BMI generally tends to increase during pregnancy[6], with successive glucose intolerance and high cholesterol levels. Examining the literature on Inositol in pregnancy, Matarrelli et al[7] reported that myo-inositol supplementation in pregnancy reduced the incidence of gestational diabetes mellitus (GDM) in women at high risk of this disorder. Also D'Anna et al[8] reported that myo-Inositol supplementation in pregnant women with a family history of type 2 diabetes may reduce GDM incidence and the delivery of macrosomic fetuses. Both studies are from a vast literature on the benefits of Inositol and its use in women with PCOS, insulin resistance and pre-diabetic states, type II diabetes, metabolic syndrome and sterility. Recently, Unfer et al[9] demonstrated and clarified that myo-Inositol is capable of restoring spontaneous ovarian activity and, as a consequence, fertility in most patients with PCOS; myo-Inositol reduces hyperandrogenemia, re-establishes a normal menstrual cycle and ovulation, thus increasing the chance of a spontaneous pregnancy. Papaleo et al[10] reported that Myo-inositol is a simple and safe treatment that is capable of restoring spontaneous ovarian activity and conse-

Table I. Baseline clinical characteristics and hematochemical parameters of two groups. Data are mean ± SD.

Variables	Control group (n = 24)	MDFM group (n = 24)	p*
Age	31.58 ± 5.66	32.2 ± 5.46	0.4854
Parity	1.04 ± 0.9	1.08 ± 0.97	0.8780
BMI	26.8 ± 0.22	26.98 ± 0.22	0.4042
Total Chol	225.54 ± 2.01	230.08 ± 2.01	0.0819
LDL	150.7 ± 11.39	163.16 ± 10.8	0.0003
HDL	74.83 ± 8.79	66.91 ± 7.64	0.0017
TG	176.29 ± 9.11	178.54 ± 7.54	0.2472
Glucose (blood)	79.70 ± 7.72	81.04 ± 5.63	0.3458
Mean pressure (systolic)	125.62 ± 6.30	122.5 ± 6.42	0.095
Mean pressure (diastolic)	83.75 ± 4.23	77.5 ± 8.34	0.002

*Statistical analysis was obtained with Student's t-test between the two group.

Table II. Comparison of clinical characteristics and hematochemical parameters of two groups at time 30 and 60 days. Data are mean ± SD.

Variables	Time = 30			Time = 60		
	Control group (n = 24)	MDFM group (n = 24)	p*	Control group (n = 24)	MDFM group (n = 24)	p*
Total Chol	225.79 ± 10.67	209.54 ± 6.6	0.0001	232.66 ± 8.82	185.37 ± 10.8	0.0001
LDL	154.16 ± 12.04	141.95 ± 12.57	0.0013	158.33 ± 11.96	124.83 ± 9.90	0.0001
HDL	71.66 ± 7.22	67.58 ± 10.80	0.0903	74.33 ± 7.68	60.54 ± 10.25	0.0001
TG	170.20 ± 10.32	154.91 ± 7.44	0.0001	175.70 ± 8.85	136.37 ± 7.63	0.0001
Glucose (blood)	82.20 ± 6.16	77.29 ± 4.05	0.0021	82.25 ± 7.15	77.41 ± 4.19	0.0064
Mean pressure (systolic)	121.04 ± 6.91	119.16 ± 6.53	0.033	119.16 ± 6.86	115.83. ± 7.89	0.125
Mean pressure (diastolic)	78.75 ± 8.10	75.20 ± 5.98	0.091	77.5 ± 10.10	75.41 ± 7.50	0.421

*Statistical analysis was obtained with Student's *t*-test between the two group.

quently fertility in most patients with PCOS. This therapy did not cause multiple pregnancies. Another study[11] evaluated retrospectively the prevalence of gestational diabetes (GD) in pregnancies evaluated after myo-inositol administration in women with polycystic ovarian syndrome in a total of 98 pregnancies in PCOS women over a 3 year period. The results suggested a possible effect of myo-inositol in the primary prevention of GD in PCOS women.

The administration of Myo-inositol has been shown to improve metabolic and hormonal pattern in PCOS patients also in a study of Gerli et al[12].

Cavalli et al[13] studied the possible effects of Inositol supplementation in a cohort of mothers at risk of producing an neural tube defects (NTD) on 15 Caucasian pregnant women from different parts of Italy with at least one previous NTD-affected pregnancy. They underwent periconceptional combined myo-inositol and folic acid supplementation. Maternal serum α-feto-protein levels were found in the normal range, and normal results on ultrasound examination were found in all the pregnancies that followed. No collateral effects or intense uterine contractions were demonstrated in this pilot study in any of the pregnancies after Inositol supplementation, and seventeen babies were born without any type of NTD[14]. Inositol phosphoglycan P-type (P-IPG), a second messenger of insulin, was reported to negatively correlate with the degree of insulin resistance in non-pregnant diabetic subjects in another study. Urinary levels of P-IPG were assessed in insulin resistant states during pregnancy such as GDM and type 2 diabetes mellitus and in normal pregnant women. The results of this investigation[15] reported that a higher P-IPG urinary excretion occurred during the second trimester in pregnant women with clinically evident insulin resistance with a positive association with poor glycemic control.

Conclusions

MDFM administration showed an improvement of all blood parameters especially after 60 days, with the exception of diastolic blood pres-

Table III. Overall comparison of clinical characteristics and hematochemical parameters in MDFM group at time 0, 30, 60 days. Data are mean ± SD.

Variables	Time = 0 (n = 24)	Time = 30 (n = 24)	Time = 60 (n = 24)	p#
Total Chol	230.08 ± 2.01	209.54 ± 6.6	185.37 ± 10.8	0.0001
LDL	163.16 ± 10.8	141.95 ± 12.57	124.83 ± 9.90	0.0001
HDL	66.91 ± 7.64	67.58 ± 10.80	60.54 ± 10.25	0.0474
TG	178.54 ± 7.54	154.91 ± 7.44	136.37 ± 7.63	0.0001
Glucose (blood)	81.04 ± 5.63	77.29 ± 4.05	77.41 ± 4.19	0.019
Mean pressure (systolic)	122.5 ± 6.42	119.16 ± 6.53	115.83. ± 7.89	0.0092
Mean pressure (diastolic)	77.5 ± 8.34	75.20 ± 5.98	75.41 ± 7.50	0.293

#Statistical analysis was obtained with Kruskal-Wallis test.

sure. MDFM could be useful in pregnancy particularly in patients with metabolic syndrome and in pre-diabetics. Other studies should confirm this preliminary study, to validate the use of this product in dyslipidemic patients with metabolic syndrome or glucose intolerance by analyzing more patients and parameters with an appropriate diet for an extended time period.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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