Curr Diab Rep (2016) 16:30
DOI 10.1007/s11892-016-0726-6

Myo-Inositol Supplementation to Prevent Gestational Diabetes Mellitus

Claudio Celentano[1] · **Barbara Matarrelli**[1] · **Peter A. Mattei**[2] · **Giulia Pavone**[1] · **Ester Vitacolonna**[3] · **Marco Liberati**[1]

Abstract Gestational diabetes mellitus (GDM) is a common complication characterized by increased insulin resistance, and by increased risk for adverse pregnancy outcomes affecting both the mother and the fetus. International guidelines describe optimal ways to recognize it, and the recommended treatment of patients affected to reduce adverse outcomes. Improving insulin resistance could reduce incidence of GDM and its complications. Recently, a few trials have been published on the possible prevention of GDM. Inositol has been proposed as a food supplement that might reduce gestational diabetes incidence in high-risk pregnant women.

This article is part of the Topical Collection on *Diabetes and Pregnancy*

✉ Claudio Celentano
ccelen@tin.it

Barbara Matarrelli
bmatarrelli@libero.it

Peter A. Mattei
pamattei@gmail.com

Giulia Pavone
pavonegiulia.gp@gmail.com

Ester Vitacolonna
evitacolonna@unich.it

Marco Liberati
liberati@unich.it

[1] Department of Obstetrics and Gynecology, University "G. d'Annunzio" Chieti, Chieti, Italy

[2] Department of Ophtalmology, University "G. d'Annunzio" Chieti, via dei Vestini, 66100 Chieti, Italy

[3] Department of Internal Medicine, University "G. d'Annunzio" Chieti, Chieti, Italy

Keywords Gestational diabetes mellitus · Insulin resistance · Myo-inositol · Prevention · Adverse pregnancy outcome

Introduction

Gestational diabetes mellitus (GDM) is a complication in pregnancy defined as any degree of carbohydrate intolerance with onset or first recognition during pregnancy [1]. Recent guidelines promote the identification of risk factors to facilitate the prompt diagnosis and management of GDM [2–4]. The introduction of food supplements that safely improve insulin resistance in pregnancy gives gynecologists the opportunity to initiate early treatment and possibly prevent GDM.

GDM is associated with an increased risk for the fetus, including macrosomia and birth injuries because of shoulder dystocia, as well as for the newborn, such as neonatal hypoglycemia, respiratory distress syndrome, and childhood obesity [5•]. Maternal risks include cesarean delivery, hypertensive disorders, and an increased risk of developing type 2 diabetes later in life. Identified risk factors for the development of GDM include maternal age, maternal body mass index (BMI), ethnic origin, family history of GDM, previous history of GDM, and previous/current adverse pregnancy outcome [1].

Recently, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, a multicentric, observational study, evaluated the relationship between maternal hyperglycemia and adverse pregnancy outcomes, and identified elevated maternal serum glucose level during pregnancy as a major risk factor for adverse pregnancy outcomes in gestations complicated by GDM. The study demonstrated a clear and consistent relationship between maternal hyperglycemia and increasing rates of large-for-gestational-age infants, fetal hyperinsulinemia, neonatal hypoglycemia, and caesarean

Published online: 22 February 2016

delivery [5•]. Furthermore, the International Association of Diabetes in Pregnancy Study Group (IADPSG) published recommendations for the diagnosis and classification of hyperglycemia during pregnancy [4].

Almost 10 % of pregnancies are complicated by GDM, and it is likely that the widespread implementation of these newly proposed criteria will more than double its prevalence.

GDM is characterized by an increase of physiological insulin resistance above that seen in pregnancies not complicated by GDM [4]. The molecular mechanism underlying insulin resistance in GDM is not fully understood. Among strategies to reduce the occurrence of GDM, insulin-sensitization with agents like metformin, has been used throughout pregnancy with contrasting results. Because of its ability to cross the placenta, fetal safety remains as a concern. Therefore, metformin is not recommended currently in the treatment of GDM [6, 7].

Myo-inositol (MI) is a cyclitol naturally present in animal and plant cells, either in its free form or as a bound-component of phospholipids or inositol phosphate derivatives. MI, or cis-1,2,3,5-trans-4,6-cyclohexanehexol, is the predominant isomeric form of inositol that is found in nature, including food items. MI was previously thought to belong to the vitamin B family; however, because it is produced in sufficient amount by the human body from D-glucose, it is no longer regarded as an essential nutrient. Human diet from animal and plant sources can contain MI in its free form, as inositol-containing phospholipid, or as phytic acid. All living cells contain inositol phospholipids in their membranes, and phytic acid is the major storage form of phosphorus in many plant tissues, particularly in bran and seeds. The greatest concentrations of MI in common foods are found in fresh fruits and vegetables, and in all foods containing seeds. Within vegetables, the highest contents of MI are observed in beans and peas, whereas leafy vegetables have the poorest content. Among fruits, cantaloupe and citrus fruits (excepted lemons) have an extraordinarily high MI content.

MI plays an important role in various cellular processes (Table 1), as the structural basis for secondary messengers in eukaryotic cells, and, in particular, as inositol triphosphates (IP_3), phosphatidylinositol phosphate lipids (PIP_2/PIP_3) and possibly inositol glycans. MI and D-chiro-inositol (DCI), another inositol isomer (Fig. 1), may also be implicated in glucose homeostasis because abnormalities in their metabolism have been associated with insulin-resistance and long-term microvascular complications in subjects with diabetes. Furthermore, given as a dietary supplement, both MI and DCI showed insulin-mimetic effects in several animal models of insulin resistance and in women with polycystic ovary syndrome. MI and DCI are involved in an array of cellular functions and abnormalities in their metabolism have been implicated in the development of several disease states, in particular in the development of insulin resistance and diabetic complications. In primary tissue sites for diabetic microvascular complications (kidney, sciatic nerve, retina, and lens), a concomitant depletion of intracellular MI and accumulation of intracellular sorbitol was commonly observed in diabetic animal models and human subjects [20••].

However, inositol (in the MI or DCI isoforms) was reported to improve insulin sensitivity and ovulatory function in young women affected by polycystic ovary syndrome [21••]. MI reduction of insulin resistance was investigated in postmenopausal women with metabolic

Table 1 MI functions

Function	Benefits
Cell survival and growth	Essential for the growth an survival of cells [5•]
Central nervous system	MI is essential for the development and function of peripheral nerves [8]
Osteogenesis	Increase calcium in bone
	Increase the bone structure strength
	MI is essential to bone formation, osteogenesis and bone mineral density [9]
Mood	MI is proposed as selective serotonin reuptake inhibitor-like role [10]
Reproduction	Restore normal ovulatory activity [11]
	Increase oocyte and egg quality [12, 13]
	Increase fertilization rate
	Increase sperm motility and mitochondrial membrane potential in vitro [14, 15]
Metabolism	Increase insulin sensitivity (reduce HOMA-IR. reduce glycemia, reduce insulinemia)
	Reduce total and LDL cholesterol
	Increase HDL cholesterol
	Reduce serum triglycerides [11, 16–19]

HDL high-density lipoprotein, *HOMA-IR* homeostatic model assessment and insulin resistance, *LDL* low-density lipoprotein, *MI* myo-inositol

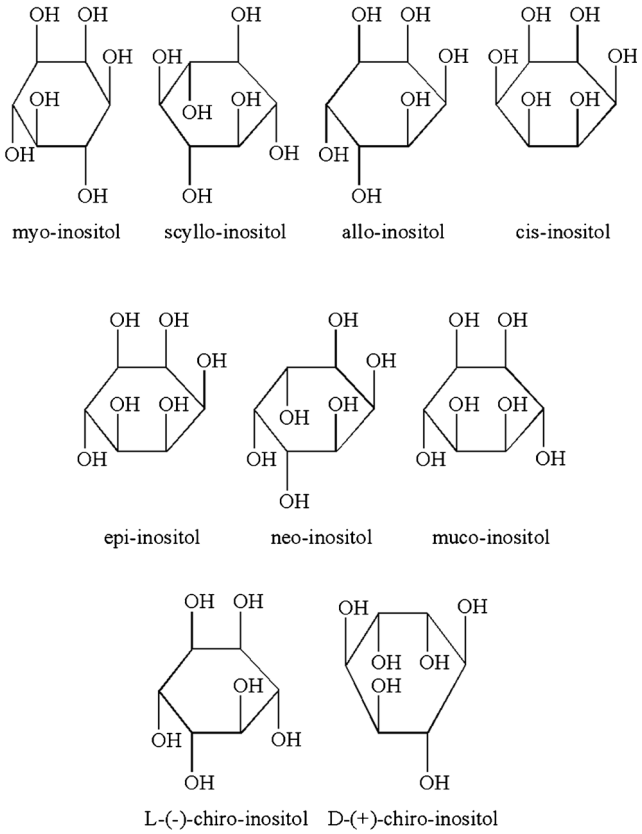

Fig. 1 Inositol stereoisomers

syndrome and in pregnant women at risk for developing or with GDM [22].

Recently, 4 randomized studies were published investigating MI in pregnant women at risk for GDM. A fifth study was recently printed on pregnant women investigating the metabolic effect of MI+DCI+manganese (Table 2). The 5 studies are summarized here.

Corrado et al 2011 [23••]

A supplement of MI (2 g twice/d) + 200 mcg folic acid (FA) twice/d (study group) vs 400 mcg FA daily (controls) was administered to pregnant women with GDM, together with a controlled diet for 8 weeks. Baseline evaluation of maternal weight, serum glucose and insulin, and consequently insulin resistance expressed as insulin resistance by homeostasis model assessment (HOMA-IR) were recorded. Starting with 93 consecutive eligible patients, 84 accepted enrollment, but only 69 were eligible for statistical analysis. Fifteen patients were lost to follow-up because they required insulin treatment when glycemic goals were not reached with diet alone (3 women in the study group and 9 in the control group). Weight gain after 8 weeks of treatment was similar in the 2 groups. Fasting serum glucose and insulin were lower in the study group exposed to MI ($P < 0.05$). HOMA-IR compared with control group was similarly reduced in the study group compared with controls ($P = 0.0001$). Adiponectin levels were reduced from basal levels in controls (12.2 ± 4.6 basal vs 11.3 ± 4.8 at 8 weeks; difference not statistically significant), whereas increased values indicative of improved metabolism were recorded in the study group (12.8 ± 5.1 basal vs 16.1 ± 6.6; $P = 0.009$) [23••].

D'Anna et al 2013 [24••]

In 220 pregnant women with a family history of type 2 diabetes within first-degree relatives, a dietary supplement of MI 4 g/d + 400 mcg FA was administered throughout pregnancy in a prospective randomized, open-label, placebo-controlled study. Controls were exposed to 400 mcg FA daily. A population of 197 patients was eligible for statistical analysis (99 in the MI group vs 98 controls). The main outcome demonstrated a statistically significant reduction of GDM diagnosed by glucose values derived from an oral glucose tolerance test (OGTT) in the MI group compared with controls (6 vs 15 patients; $P = 0.04$). MI exposure significantly reduced fasting and 1-hour glycemia at OGTT ($P = 0.001$ and $P = 0.02$, respectively). Offspring of control women had a higher birth weight (3273 ± 504 g vs 3111 ± 447 g in the control and study groups, respectively; $P = 0.02$), whereas the gestational age at delivery was similar (275 ± 12 days vs 274 ± 11 days in control and MI groups, respectively; P = NS). Seven newborn in the control group and none in the study group presented macrosomia defined as birth weight above 4000 g ($P = 0.007$)[23••].

Matarrelli et al 2013 [25••]

A total of 84 consecutive nonobese pregnant women with elevated maternal serum glucose levels, defined as glycemia within 5.1 and 7.0 mmol/L (92–126 mg/dL), were considered eligible for a prospective, randomized, placebo controlled, double-blind study. The study group was exposed to 2 g MI + 200 mcg FA twice a day and controls were exposed to 200 mcg FA twice a day. Thirty-five participants completed follow-up in the study group and 38 in the control group. The primary outcome evaluation demonstrated a significant reduction of abnormal maternal glucose levels by OGTT (2 vs 27 patients; $P = 0.001$). Glycemic values at 0 and 60 minutes were significantly higher in controls compared with women in the study group ($P = 0.001$ and $P = 0.04$, respectively). Insulin therapy was needed in 1 case in the study group vs 8 cases in the control group ($P = 0.053$). Similarly, a nonsignificant

Table 2 Summary of the characteristics of the principle studies on the effect of MI supplements for preventing GDM

Authors	Study design	Time	Treatment	No. of subjects	Inclusion criteria	Exclusion criteria	Outcomes	Results
Corrado et al 2011 [23••]	Randomized controlled vs FA Open label	8 wk	2 g MI + 200 mcg FA twice/d	N = 69 Placebo: 45 MI: 24	GDM (OGTT at 24–28 wk)	Insulin therapy, premature delivery before 35 wk gestation	Fasting HOMA-IR	Fasting glucose and insulin, consequently HOMA-IR, decreased in both groups (50 % in MI group vs 29 % in controls), but the decrease in MI was significantly greater ($p = 0.0001$). Adiponectin increases in the MI group while decreased in controls ($p = 0.009$)
D'Anna et al 2013 [24••]	Randomized controlled vs FA Open label	From the 1st trimester through the whole pregnancy	2 g MI + 200 mcg FA twice/d	N = 220 Placebo: 110 MI: 110	First degree relatives affected by type 2 diabetes Prepregnancy BMI <30 Fasting plasma glucose <126 and random glycemia <200 Single pregnancy Caucasian ethnic background	Pre-pregnancy BMI > o = 30 Previous GDM Pre-gestational diabetes First trimester glycosuria First-degree relatives not affected by type 2 diabetes fasting and random glycemia >126 or 200 Twin pregnancies Steroids therapy PCOs women Not Caucasian	Incidence of GDM; Prevalence of fetal macrosomia (fetal weight > 4000 g at delivery), caesarean section, gestational hypertension, preterm delivery, neonatal hypoglycemia, shoulder dystocia and distress respiratory syndrome	Incidence of GDM reduced in the MI group compared with the placebo group: 6 vs 15.3 %, respectively ($P = 0.04$) and reduction of GDM risk occurrence (odds ratio 0.35). Significantly reduced fasting ($p < 0.001$) and hyperglycemia ($p < 0.02$) at OGTT in the MI group. A statistically significant reduction of mean fetal weight at delivery in MI group and absence of fetal macrosomia (vs 7 cases in placebo group). No difference between the groups for the other secondary outcomes studied
Matarrelli et al 2013 [25••]	Randomized controlled vs FA Double-blind	For the entire pregnancy	2 g MI + 200 mcg FA twice/d	N = 75 Placebo: 39 MI: 36	Singleton pregnant women with an elevated fasting	Pre-gestational obesity (BMI > 35) and refusal to	OGTT at 24-28 wk gestation, BMI, need for	The incidence of GDM in mid pregnancy was significantly

Table 2 (continued)

Authors	Study design	Time	Treatment	No. of subjects	Inclusion criteria	Exclusion criteria	Outcomes	Results
					glucose (glycemia 92–126) in the 1st or early 2nd trimester	participate	maternal insulin therapy, macrosomia, polyhydramnios, neonatal birth weight and hypoglycemia	reduced ($p = 0.001$) in women who received MI compared with placebo (relative risk 0.127). Women supplemented with MI required less insulin therapy, delivered at a later gestational age, had significantly smaller babies with fewer episodes of neonatal hypoglycaemia.
Malvasi et al 2014 [21••]	Randomized controlled vs placebo Double-blind	20 d	2 g MI + 400 mcg DCI + 400 m-cg FA + 10 mg manganese/d	N = 65 Placebo: 24 Drug: 24	Healthy pregnancies 13–24 wk gestation, BMI 25–30, 30–40 y old women	Pre-gestational diabetes, cardiovascular diseases, chronic hypertension, autoimmune diseases, dysthyroidism	Blood pressure, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glycemia basally, at 30 d, and at 60 d	Significant reduction of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides and systolic blood pressure were recorded in treatment group
D'Anna et al 2015 [26••]	Randomized controlled vs FA Open label	From the 1st trimester through the whole pregnancy	2 g MI + 200 mcg FA twice/d	N = 220 Placebo: 110 MI: 110	Obese patients (BMI >30) 18–45 y-old Fasting glucose <126	BMI <30 Fasting glucose >126 Previous GDM Twin pregnancy Pre-gestational diabetes Steroids therapy	Incidence of GDM at OGTT and HOMA-IR were evaluated (as main outcomes). Cesarean delivery, gestational hypertension, preterm delivery, shoulder dystocia, macrosomia, neonatal hypoglycemia, NICU transfer as secondary outcomes.	Significant reduction of GDM was described in MI group (14.0 vs 33.6 %; $p = 0.001$). HOMA-IR in controls was -1.0 ± 3.1 vs 0.1 ± 1.8 ($p = 0.048$). Reduction of GDM risk by 66 % (excluding type 2 diabetes in family the risk reduction was 77 %.

BMI body mass index, *DCI* D-chiro-inositol, *FA* folic acid, *GDM* gestational diabetes mellitus, *HDL* high-density lipoprotein, *HOMA-IR* homeostatic model assessment and insulin resistance, *LDL* low-density lipoprotein, *MI* myo-inositol, *N* number, *NICU* neonatal intensive care unit, *PCOS* polycystic ovary syndrome, *OCTT* oral glucose tolerance test

trend toward increased amniotic fluid was recorded in 7 controls vs 1 MI exposed fetus ($P = 0.07$). Maternal weight gain, expressed as an increase in BMI, was significantly higher in controls compared with women in the study group (3.8 ± 2.4 and 2.3 ± 1.1, respectively: $P = 0.001$). Fetal biometry at time of OGTT demonstrated an increased abdominal circumference expressed as percentile in controls (65.6 vs 41.7; $P = 0.001$). Also biparietal diameter was different in the 2 groups (71.6 vs 61.2 in fetuses from the study group and control fetuses respectively; $P = 0.04$), probably because of the different incidence of breech fetuses in the population examined. Gestational age at delivery was significantly lower in controls (37.2 vs 39.3; $P = 0.001$), possibly because of better metabolic control of patients. Birth weight was similar in the 2 populations (3267 vs 3251 g in the MI and control groups respectively; $P = 0.12$); however, birth weight expressed as percentiles was significantly higher in controls compared with the study group (56.6 and 42.8, respectively; $P = 0.001$). The absolute risk reduction for the primary outcome was 66.3 % and the "Number-Needed-to-Treat" was 2 (95 % CI, 1.2–2.0) [25••].

Malvasi et al 2014 [21••]

The dietary supplement MI, FA, and manganese (MDFM) was tested in a prospective, randomized, double-blind, placebo-controlled study. Sixty-five healthy pregnant women were enrolled; 48 reached all inclusion criteria and completed follow-up. MDFM (2 g MI + 400 mcg DCI + 400 mcg FA + 10 mg manganese) were administered for 20 days. Maternal blood pressure (systolic and diastolic), BMI, serum glucose, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides were evaluated at baseline, and after 30 and 60 days. At baseline clinical characteristics of the MDFM group presented differences as diastolic blood pressure (77.5 vs 83.7 mm Hg; $P = 0.002$), LDL-cholesterol (163.16 vs 150.70 mg/dL; $P = 0.0003$), and HDL-cholesterol (66.91 vs 74.83 mg/dL; $P = 0.0017$) compared with controls. At 30 and 60 days, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and blood pressure (systolic and diastolic) were reduced in the MDFM group. Statistical significance was reached at 30 days for total cholesterol, LDL-cholesterol, triglycerides, glycemia, and systolic blood pressure. At 60 days, statistical significance was reached for total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, and glycemia. The overall comparison of clinical characteristics showed a statistically significant reduction of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, and systolic blood pressure [21••].

D'Anna et al 2015 [26••]

A randomized, open-label, placebo controlled study was recently published on insulin resistance in obese pregnant women exposed to MI. 220 obese (BMI >30) patients were enrolled at 12.13 weeks of gestation in 2 Italian hospitals. A total of 110 patients were exposed to 2 g MI + 200 mcg FA twice/d (study group), and 110 patients were exposed to 200 mcg FA twice/d (control group) throughout the pregnancy. The GDM rate was significantly reduced in study group compared with control (14.0 % vs 33.6 % respectively; $P = 0.001$). Furthermore, women treated with MI showed a significantly greater reduction in HOMA-IR compared with the control group (-1.0 ± 3.1 vs -0.1 ± 1.8; $P = 0.048$). The risk reduction of GDM in MI-exposed patients was 66 % (OR 0.34 [0.17–0.68]) compared with controls. After excluding patients with a positive family history ("parents with type 2 diabetes mellitus") the risk reduction was 77 % (OR 0.23 [0.10–0-53]). The logistic regression analysis demonstrated that only MI treatment was independently associated with the onset of GDM ($P = 0.03$). Within secondary outcomes gestational hypertension ($P = 0.02$) and neonatal transfer to the neonatal intensive care unit ($P = 0.03$) were statistically reduced in the MI group. Preterm delivery showed a nonsignificant trend toward higher rates in controls (9.6 % vs 3.1 %; $P = 0.06$) [26••].

Conclusions

MI is a polyol naturally present in eukaryotic cells and is a component of numerous organic molecules, which makes it essential for numerous biological processes. Since these molecules include second messengers, and some of these are putative mediators of insulin action, their deficit in insulin target tissues probably contributes to the progressive development of insulin resistance [20••]. Dietary supplement of inositol isomers have been found to lower postprandial plasma glucose levels in several animal models of diabetes or insulin resistance [28–30]. The insulin-mimetic properties of dietary inositol supplements is thought to be mainly related to the production of inositol glycan secondary messengers containing either MI or DCI [20••]. Nevertheless, further investigations are required to disclose the exact molecular mechanisms of MI actions. Randomized controlled trials of MI dietary supplementation have shown positive results in terms of reducing insulin resistance, incidence of GDM and its adverse outcomes. However, larger studies in double-blind trials including populations with ethnic backgrounds other than Caucasian, evaluating different stereoisomers effects, and postnatal long-term effects are needed.

Compliance with Ethical Standards

Conflict of Interest Claudio Celentano, Barbara Matarrelli, Peter A. Mattei, Giulia Pavone, Ester Vitacolonna, and Marco Liberati declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article contains a study with human subjects performed by some of the authors. The paper for reference 30 received local ethical committee approval and clinical trial registration as described in the M&M section.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Buchannan TA, Xiang AH. Gestational diabetes mellitus. J Clin Invest. 2005;115:485–91.
2. Corrado F, Pintaudi B, Di Vieste G, et al. Italian risk-factor based screening for gestational diabetes. J Matern Fetal Med. 2014;27: 1445–8.
3. Ten WT, Teede HJ, Paul E, et al. Risk factors for gestational diabetes mellitus: implications for the application of screening guidelines. Aus N Z J Obstet Gynaeocol. 2011;51:26–30.
4. Ryan EA. Diagnosis gestational diabetes. Diabetologia. 2011;54: 480–5.
5. • HAPO study Cooperative research Group, Metger B, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358:1991–2002. **The present study represents the mainstay of a new era in gestational diabetes diagnosis**.
6. Geimlueck CJ, Panikoff J, Aregawi D, et al. Prevention of gestational diabetes by metformin plus diet in patients with polycystic ovary syndrome. Fertil Steril. 2088;89:625–34.
7. Vanky E, Stridklev S, Heimstad R, et al. Metformine versus placebo from first trimester to delivery in plycystic ovary syndrome: a randomized controlled multicenter study. J Clin Endocrinol Metab. 2010;95:E445–8.
8. Chau JFL, Lee JWS, Law SK, et al. Sodium/myo-inositol cotransporter-1 is essential for the development and function of the peripheral nerves. FASEB J. 2005;19:1887–9.
9. Dai Z, Chung D, Miao KS, Lau AWH. Sodium/myo-inositol cotransporter-1 and myo-inositol are essential for osteogenesis and bone formation. J Bone Miner Res. 2011;26:582–90.
10. Carlomagno G, Unfer V, Buffo S, et al. Myo-inositol in the treatment of premenstrual dysphoric disorder. Hum Psychopharmacol. 2011;26:526–30.
11. Unfer V, Carlomagno G, Dante G, et al. Effects of myo-inositl in women with PCOs: a systematic review of randomized controlled trials. Gynecol Endocrinol. 2012;28:569–75.
12. Ciotta L, Stradacquadanio M, Pagano I, et al. Effects of myo-inositol supplementation on oocyte's quality in PCOs patients: a double blind trial. Eur Rev Med Pharmacol Sci. 2011;15: 509–14.
13. Unfer V, Carlomagno G, Rizzo P, et al. Myo-inositol rather than D-chiro-inositol is able to improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Eur Rev Med Pharmacol Sci. 2011;15:452–7.
14. Condorelli RA, La Vignera S, Di Bari F, et al. Effects of myoinositol on sperm mitochondrial function in-vitro. Eur Rev Med Pharmacol Sci. 2011;15:129–34.
15. Condorelli RA, La Vignera S, Bellanca S, et al. Myoinositol: does it improve sperm mitochondrial function and sperm motility? Urology. 2012;79:1290–5.
16. Santamaria A, Giordano D, Corrado F, et al. One-year effects of myo-inositol supplementation in post-menopausal women with metabolic syndrome. Climateric. 2012;15:490–5.
17. Croze ML, Vella RE, Pillon NJ, et al. Chronic treatment with myo-inositol reduces white adipose tissue accretion and improves insulin sensitivity in female mice. J Nutr Biochem. 2013;24:457–66.
18. Maeba R, Hara H, Ishikawa H, et al. Myo-inositol treatment increases serum plasmaogens and decreases small dense LDL, particularly in hyperlipidemic subjects with metabolic syndrome. J Nutr Sci Vitaminol. 2008;54:196–202.
19. Ortmeyer HK. Dietary myoinositol in lower urine glucose and in lower postprandial plasma glucose in obese insulin resistant rhesus monkeys. Obes Res. 1996;4:569–75.
20. •• Croze L, Soulage C. Potential role and therapeutic interests of myo-inositol in metabolic diseases. Biochimie. 2013;95:1811–27. **The present review represents a complete description of myo-inositol in medicine**.
21. •• 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;18:270–4. **This is the first description of different inositol stereoisomers in pregnancy**.
22. Saltier AR. Second messenger of insulin action. Diabetes Care. 1990;13:244–56.
23. •• Corrado F, D'Anna R, Di Vieste G. The effect of myoinositol supplementation on insulin resistance in patients with gestational diabetes. Diabet Med. 2011;28:972–5. **The present study is a controlled trial in GDM treatment with myo-inositol**.
24. •• 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. Diabetes Care. 2013;36: 854–7. **This study compared myo-inositol and placebo in a high-risk population.**
25. •• Matarrelli B, Vitacolonna E, D'Angelo, 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;26:967–72. **This is a controlled double-blind controlled trial**.
26. •• D'Anna R, Di Benedetto A, Scilipoti A. Myo-inositol supplementation for prevention of gestational diabetes in obese pregnant women. Obstet Gynecol. 2015;126:310–5. **The study exposed obese pregnant women to myo-inositol**.
27. Kennington AS, Hill CR, Craig J, et al. Low urinary chiro-inositol excretion in noninsulin-dependent diabetes mellitus. N Engl J Med. 1990;323:373–8.
28. Ortmeyer HK, Huang LC, Zhang L, et al. Chiroinositol deficiency and insulin resistance acute effects of D-Chiroinositol administration in streptozotocin-diabetic rats, normal rats given a glucose load, and spontaneously insulin-resistance rhesus monkeys. Endocrinology. 1993;132:646.
29. Ortmeyer HK, Huang LC, Zhang L. Effects of D-chiroinositol added to a meal on plasma glucose and insulin in hyperinsulinemic rhesus monkeys. Obes Res. 1995;3 Suppl 4:605S–8.
30. Ortmeyer HK. DIetary myo-inositol results in lower urine glucose and in lower post-prandialplasma glucose in obese insulin resistant rhesus monkey. Obes Res. 1996;4:569–75.