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Review

Results from the International Consensus Conference on Myo-inositol and D-chiro-inositol in Obstetrics and Gynecology: the link between metabolic syndrome and PCOS

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ABSTRACT

In recent years, interest has been focused to the study of the two major inositol stereoisomers: myo-inositol (MI) and D-chiro-inositol (DCI), because of their involvement, as second messengers of insulin, in several insulin-dependent processes, such as metabolic syndrome and polycystic ovary syndrome. Although these molecules have different functions, very often their roles have been confused, while the meaning of several observations still needs to be interpreted under a more rigorous physiological framework.

With the aim of clarifying this issue, the 2013 International Consensus Conference on MI and DCI in Obstetrics and Gynecology identified opinion leaders in all fields related to this area of research. They examined seminal experimental papers and randomized clinical trials reporting the role and the use of inositol(s) in clinical practice.

The main topics were the relation between inositol(s) and metabolic syndrome, polycystic ovary syndrome (with a focus on both metabolic and reproductive aspects), congenital anomalies, gestational diabetes.

Clinical trials demonstrated that inositol(s) supplementation could fruitfully affect different pathophysiological aspects of disorders pertaining Obstetrics and Gynecology. The treatment of PCOS women as well as the prevention of GDM seem those clinical conditions which take more advantages from MI supplementation, when used at a dose of 2 g twice/day.

The clinical experience with MI is largely superior to the one with DCI. However, the existence of tissue-specific ratios, namely in the ovary, has prompted researchers to recently develop a treatment based on both molecules in the proportion of 40 (MI) to 1 (DCI).

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Contents

Introduction

Metabolic syndrome (MS) is a combination of disorders characterized by alterations in carbohydrate metabolism, obesity, systemic arterial hypertension and dyslipidemia, which increase the risk of developing cardiovascular disease and diabetes. Metabolic disorders affect reproductive function controlled by the hypothalamus and the pituitary.

A clinical example of such an interaction is represented by *Polycystic ovary syndrome* (*PCOS*) one of the most common female endocrine/reproductive disorders.

Despite its pathophysiology remains still unclear, the role of insulin resistance as the main driver has been highlighted in recent years, in addition to genetic and environmental causes.

Insulin resistance contributes both to metabolic features and to reproductive features [1,2], underlying many phenotypes described for PCOS patients.

Since women with PCOS share symptoms with the MS, lifestyle changes are the key, first-line treatment strategy for their management [3]. However, compliance of such intervention is often reduced and effects unsatisfactory, thus requiring the addition of insulin-sensitizing drug (ISD).

Metformin and *thiazolidinediones* are the main available ISD. Due to the eventual weight gain and cancer risks of thiazolidinediones, prescription of these drugs has been limited only to diabetic patients [4]. In women with PCOS, treatment with metformin ameliorated the cardio-metabolic profile by improving insulin sensitivity, lowering blood glucose and androgen levels, possibly acting through body weight changes [5–8]. Metformin is more active than oral contraceptives in reducing fasting insulin not increasing triglycerides whereas it is less effective in improving menstrual pattern and correcting hyperandrogenism [9]. Metformin is also a reasonable option for those women who cannot use oral contraceptives. The main limitations to metformin use are its gastrointestinal side effects (abdominal discomfort, nausea, and diarrhea) and the need to monitor hepatic and renal function [4]. Hence, patients' compliance remains an issue as for lifestyle changes.

Inositols

The discovery that the impairment in the insulin signaling could be due to a defect in the inositolphosphoglycans (IPGs) second messenger pathway opened new horizons in the clinical management of PCOS. IPGs are involved in activating enzymes that control glucose metabolism [10]. In PCOS women, a defect in tissue availability or altered metabolism of inositol and/or IPGs mediators may contribute to insulin resistance [11].

Inositol (*INS*) and their derivatives are found especially in fruits and beans, where they are generally present in the form of phytic acid or its salts (phytates). INS is a hexahydroxycyclohexane, chemically represented by a stereo isomeric family of 9 inositols, among which myo-inositol (MI) is the most widely distributed in nature.

INS is basically incorporated into cell membranes as phosphatidyl-myo-inositol, the precursor of inositol triphosphate (Ins-1,4,5P3, InsP3), which acts as second messenger, regulating the activities of several hormones such as FSH, TSH, and insulin [12,13].

Whereas intracellular INS pool is almost (>99%) constituted by MI in most tissues, significant differences have been recorded in the concentration of MI and D-chiro-inositol (DCI), another important stereoisomer, in fat, muscle and liver. This different distribution reflects the distinct functions that likely the two isomers are playing in those tissues, and their respective proportions are actively maintained as MI is enzymatically transformed into DCI through a NAD, NADH-dependent epimerase, according to tissue requirement, the enzymatic reaction stimulated by insulin [14].

In particular, MI is essential in ensuring proper oocyte maturation [15,16], and it was demonstrated that culturing embryos in media enriched with MI, embryos have a more physiological cleavage rate and an increased number of expanded blastocyst [17].

Overall these results demonstrated a relevant physiological role of INS and its metabolites in human reproduction [18] so that INS supplementation was proposed as a novel treatment in women affected by PCOS.

The impetuses for these studies rely on the well-known correlation between metabolic syndrome and PCOS, as well as the observed defects in INS metabolism in PCOS and the implication of INS in insulin signal transduction. Indeed, it is widely acknowledged that both insulin insensitivity and metabolic syndrome are prominent features in a consistent proportion of patients affected by PCOS. Furthermore, metabolic syndrome is one of the major risk factors for cardiovascular diseases.

Conference purpose and method

Clinical studies evaluating INS effects in Obstetrics and Gynecology appeared in the literature of the last 10 years, but few systematic reviews and a Cochrane meta-analysis tried to summarize their effects. In such situation, some confusion arose, *i.e.*, classifying in a wrong way the content of inositol supplement in some study. Moreover, since the growing interest in such topic, several new studies and researches were published, that were not previously assessed.

In order to place a milestone and to open some reflection points on this issue, the PREIS School (Permanent International and European School in Perinatal Neonatal and Reproductive Medicine) organized the "2013 Florence International Consensus Conference on myo and D-chiro-inositol in obstetrics and gynecology". To this purpose, the PREIS Chairman, GDR, identified opinion leaders in the fields of cell biology (GC, MB, CS, PC), mammalian embryology (AB, TTC), human endocrinology (AL, SB), metabolism (RDA, ZAK), obstetrics and gynecology (FF, SG, MMO, PD, MH), who have expertise in INS physiology, biochemistry, pharmacology and clinical effects.

According to specific expertise, the nominated Scientific Committee divided into two separate panels with the aim at reviewing updated information on the role of INS in the field of obstetrics and gynecology on one side, and in the field of assisted reproduction on the other side. The results of the latter panel are separately reported [19].

The panel of Obstetrics and Gynecology nominated FF as Chairmen and PC as Secretary. They set the list of research questions (Table 1).

In order to answer these questions, the panel examined seminal experimental papers and clinical trials reporting the role and the use of INS in clinical practice with randomized controlled trials (RCTs) selected by the Organizing PREIS School. A preliminary statement containing the panel's recommendations was drawn and agreed during the Conference, and it represents the basis of the present conclusive paper, redacted by FF, MB and SB, taking into consideration the guidelines of the Italian Ministry of Health and National Institute of Health.

Results

1. Could inositol(s) be considered a further approach to metabolic syndrome?

Metabolic syndrome is defined by the presence of three of the following factors: abdominal obesity (waist circumference >102 cm in men or >88 cm in women); triglycerides >150 mg/dL; HDL cholesterol (<40 mg/dL in men or <50 mg/dL in women); blood pressure above 130/85 mmHg; fasting glucose >110 mg/dL.

Therefore, the treatment needs to be multilevel and should target the different clinical aspects of the syndrome. A general consensus already exists on the first line approach that should be the lifestyle modifications (diet, physical exercise, regular sleep period). However, implementation of behavioral changes cannot be easily reached by every patient and/or in every situation, determining poor compliance.

Since insulin resistance is the main driver of the metabolic syndrome, the use of insulin sensitizer is therefore well established, in order to reduce comorbidities that characterize the metabolic syndrome [5].

Although INS have indeed an insulin sensitizing action, only one trial is available and has to be highlighted that such study was carried out in postmenopausal women. Eighty patients were prescribed diet, then randomized to receive additional MI 4 g/day or nothing, for 12 months. Those ones supplemented with MI reported a significant reduction of Homeostasis Model Assessment (HOMA) index, fasting insulin and blood glucose level, respect to controls (diet only) [20,21].

Table 1
Research question identified by the panel of Obstetrics and Gynecology.

1. Could inositol(s) be considered a further approach to metabolic syndrome?
2. Is inositol(s) dysregulation involved in nurturing PCOS?
3. Does inositol(s) supplementation correct PCOS metabolic aspects?
4. Does inositol(s) supplementation improve PCOS reproductive aspects?
5. Does inositol(s) have a role in congenital anomalies?
6. Is there any evidence that inositol(s) affects gestational diabetes?

2. Is inositol(s) dysregulation involved in nurturing PCOS?

Epimerase activity dysregulation affects MI/DCI ratio and could impair hormone signaling such as insulin and FSH. Literature findings are consistent in demonstrating a defect in tissue availability and/or utilization of MI and/or DCI women with in PCOS. This would likely contributes to the insulin resistance typical of the syndrome [14,22], also considering that the two main INS stereoisomers showed distinct role in the insulin signaling. DCI is mainly involved in the glycogen synthesis (liver, fat and muscle), while MI is responsible for the activation of gluco-transporters and glucose utilization [14].

At ovarian level, DCI is responsible for the insulin-mediated testosterone overproduction [23] whereas MI is involved in the FSH signaling [24,25]. Based on the fact that the epimerase activity, regulating the ratio MI/DCI, is insulin dependent, whereas ovaries never become insulin resistant (as it occurs in muscles and liver) it has been speculated that PCOS patients likely present an enhanced MI to DCI epimerization into the ovary. This would result in overproduction of DCI and in MI deficiency [24].

The above hypothesis has been proven by two independent laboratories. The first laboratory reported that "in vitro" theca cells collected from PCOS women showed an increased epimerase activity respect to controls [14]. The second one measured the concentration of MI and DCI in follicular fluids collected from healthy and PCOS women, overall 40 (20 + 20). Authors reported a MI/DCI ratio of 100:1 in the control sample, whereas the ratio dropped to 0.2:1 in the PCOS samples [22]. Both studies demonstrated that the ovary of PCOS women suffers from a specific MI depletion and a DCI overload. This depletion would have been responsible for the poor oocyte quality observed in PCOS patients and would have impaired the FSH signaling [25,26].

3. Does inositol(s) supplementation correct PCOS metabolic aspects?

Both DCI and MI have shown to be effective in ameliorating PCOS metabolic aspects. Data on DCI have been reported in two different trials involving 32 patients while data on MI have been reported in four trials involving 301 patients [27–31]. Indeed, both INS improved insulin resistance and dyslipidemia. More recently two studies reported the effects of a combined supplement containing both MI + DCI in their physiological plasma ratio 40:1. The open study showed a reduction of LDL-cholesterol and insulin levels, as well as HOMA index in 20 obese PCOS women after 24 weeks [29]. The RCT compared MI alone with combined treatment for a duration of 6 months in 50 women with PCOS (BMI > 27 kg/m^2). The latter allows a quicker normalization of glucose metabolism compared to MI alone [28]. Since the balanced ratio of the two molecules is crucial for proper tissue function, a treatment based on the association of MI and DCI in the physiological ratio seems to be the most appropriate.

4. Does inositol(s) supplementation improve PCOS reproductive aspects?

MI treatment has been shown to ameliorate the reproductive morbidities affecting PCOS women, *i.e.*, hormone changes, irregular menstrual cycle, anovulation and infertility. In particular, MI has been able to reduce androgen levels (testosterone and androstenedione), correct the FSH/LH ratio and induce ovulation witnessed by adequate luteal phase progesterone production. Such changes are paralleled by clinical improvements, *i.e.*, a

restoration to normal menstrual cycle rhythm (as long as the treatment is performed) and the achievement of pregnancy by timed intercourse, in absence of hormone stimulation [32].

On the contrary, the data are not so clear for the DCI. Indeed, in the first study an improvement both on one-time ovulation and on the hormonal profile in PCOS women has been reported. Unfortunately, the same research group, doubling the DCI dosage, was not able to replicate the previous result, only confirming beneficial metabolic effects reporting a direct correlation between glucose-stimulated DCI-IPG release and insulin sensitivity [33,34].

5. Does inositol(s) have a role in congenital anomalies?

Starting in the late 80s, some studies carried out in Chicago evidenced that, improving MI content *in vitro*, congenital anomalies could be avoided.

The importance of MI for supporting embryogenesis was further highlighted by others able to identify a threshold value of MI in the serum below which pregnancy would have turned into an abortion [35]. Moreover, in a mouse model of folic acid resistant neural tube defects (NTD), MI was able to prevent NTD formation. On these ground, a proof of concept study was carried out in a group of patients at high risk of NTD (*i.e.*, folic acid resistant: women that had a NTD pregnancy despite proper folic acid prophylaxis). Caucasian women were treated with folic acid and MI allowing 17 babies born without malformations [36–38].

In order to draw a final word on this topic, an international trial, *i.e.*, the PONTI (Prevention Of Neural Tube defects by Inositol) study based at the University College of London has been organized and it is still ongoing.

6. Is there any evidence that inositol(s) affects gestational diabetes?

Because of their features, inositol(s) represent an effective treatment for GDM. Five studies (4 RCTs) addressed this issue [39–43].

None of them involved DCI. MI was supplied at the same dose and compound in all studies (myo-inositol 2 g + folic acid 200 μg, twice/day). The control arm was folic acid 400 μg/day. The rate of GDM was significantly reduced by MI supplementation in women presenting at 1st trimester with elevated fasting blood glucose or with a positive family history of Type 2-Diabetes Mellitus or being obese.

Summarizing the data, 86 patients on 233 in the control group developed GDM while only 22 on 211 in the treated group (OR = 0.20; 95%C.I.: 0.11–0.34). Therefore, MI reduced the risk of developing GDM by 80%.

Moreover, in women already affected by GDM, the glucose homeostasis improved in those patients receiving MI [40]. Two of the studies also reported that MI treated women gave birth to less macrosomic babies. The rate of preterm birth and gestational hypertension remained unchanged. Unfortunately, the studies were underpowered for any other outcome except GDM diagnosis.

Conclusions

Despite the growing interest toward INS as documented by the increasing number of studies appearing in the literature, few definitive conclusions implying clinical practice could be drawn.

Nonetheless, the experimental data actually give convincing support to the notion that both MI and DCI are involved in several biological pathways, namely those related to the transduction of Insulin signal.

Clinical data demonstrated that inositol(s) supplementation could fruitfully affect different pathophysiological aspects of disorders pertaining Obstetrics and Gynecology. The treatment of PCOS women as well as the prevention of GDM seem those clinical conditions which take more advantages from MI supplementation, when used at a dose of 2 g twice/day.

The clinical experience with MI is largely superior to the one with DCI. However, the existence of tissue-specific ratios, namely in the ovary, has prompted researchers to recently develop a treatment based on a MI/DCI combination (ratio 40:1). Such approach seems promising.

Knowledge on INS use in Obstetrics and Gynecology should be increased in the future, either summarizing available data in a meta-analysis or performing larger multicenter trials. RCTs are especially required to explore the potential of MI/DCI combination treatment in selected phenotypes of PCOS women as well on the diverse aspect of metabolic syndrome. Moreover, epimerase regulation as well as the individual role of MI, DCI and their combination in both theca and granulosa cells should be object of intensive laboratory investigations.

Conflict of interest

Dr. Gianfranco Carlomagno declares that he is employee at Lo.Li. Pharma, Rome. The other authors declare that they have no conflicts of interest in connection with this article.

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