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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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[1] The scientific board of the International Consensus Conference on inositols.

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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.