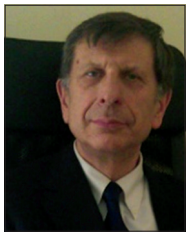
GUEST EDITORIAL

Pretreatment with Myo-Inositol in Patients Undergoing Gonadotropins Multiple Follicular Stimulation for IVF



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Myo-inositol is an isomer of a C6 sugar alcohol that belongs to the vitamin B complex group.[1] Myo-inositol (MI) is one of the nine 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 D-chiro-inositol (DCI), which is not synthesized from precursors in the body but obtained from epimerization of Myo Inositol.[2] In stereochemistry, epimer refers to one of a pair of stereoisomers. The two isomers differ in configuration at only one stereogenic center. All other stereocenters in the molecules, if any, are the same in each. Epimerisation is a chemical process where an epimer is transformed into its chiral counterpart.

Biochemical studies have shown that the Myo Inositol (MI) stereoisomers are specifically involved in the correct activation of the insulin receptor as well as in the transduction of the message (second messenger) able to activate intracellular metabolic processes of glycolysis.

Some studies suggested that MI could play an important role in cellular morphogenesis and cytogenesis, in the synthesis of lipids, in the creation of cell membranes and in cell growth.[3,4] It is also a precursor of phospholipids, which are responsible for the generation of important intracellular signals in mammalian oocytes and in the resumption of meiotic maturation.[5-7]

Pretreatment with MI of patients who undergo multiple follicular stimulation for IVF has become a common tool.

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There is a large literature on the pre-treatment of PCOS patients and a minor literature in patients who do not have endocrine disorders

Pretratment in Patiens PCOS Undergoing IVF

The syndrome affects up to 10% of women of reproductive age, and is the most common cause of infertility in industrialized countries.[8] Its current definition requires the presence of two of the three following criteria: (1) chronic oligo-ovulation or anovulation, (2) hyperandrogenism (either clinically established or confirmed by laboratory testing); and (3) the presence of _12 follicles measuring 2–9mm in diameter in each ovary and/or increased ovarian volume (_10 ml), detected by ultrasound examination.[9] PCOS is often associated with profound insulin resistance as well with the related compensatory hyperinsulinemia. The association with hyperinsulinemia and PCOS has become clear since 1980.[10] These abnormalities, together with obesity, explain the substantially increased prevalence of glucose intolerance in PCOS.[11] Recently, the role of myo-inositol has powerfully emerged in the pathogenesis of polycystic ovary syndrome (PCOS), in particular linked with insulin resistance. In fact, some of the actions of insulin are mediated by putative inositol-containing phosphoglycan (IPG) mediators, also known as putative insulin mediators or second messengers. These mediators are generated by hydrolysis of glycosylphosphatidylinositol lipids and/or proteinated species located in the outer leaflet of the cell membrane. Two different IPG have been identified: (i) the D-chiro-IPG mediator, which activates pyruvate dehydrogenase phosphatase, and (ii) the MYO-IPG which inhibits cyclic AMP-dependent protein kinase.[12,13] A positive role of myo-inositol in insulin-resistant women with PCOS could depend on defects in the insulin IPG-mediated signaling pathway, that seems to be primarily implicated in the pathogenesis of insulin resistance in

this clinical setting.[14,15] Accordingly, MI has been classified as an insulin sensitizing agent and it is commonly used in PCOS treatment.[16-18] By rescuing the ovarian response to endogenous gonadotropins, myo-inositol reduces perandrogenemia and reestablishes menstrual cyclicity and ovulation, increasing the chance of a spontaneous pregnancy.[19,20] Its use in human is safe and only the highest dose (12 g/day) induced mild gastrointestinal side effects such as nausea, flatus and diarrhea.[21]

Some authors tested the effect of myo-inositol in IVF protocols with PCOS patients. Pretreatment with inositol had a variable duration: from beginning of pretreatment with GnRH analogue[22-24] up to 3 months of pre-treatment.[25,26] These authors agree in reporting an increased recovery of Met II oocytes, a decreased use of IU FSH to reach follicular maturity. They also report a positive trend in pregnancy rate and in implantetion rate.

Has been also demonstrated[27] that myo-inositol is effective in preventing OHSS, similar to metformin; administration of myo-inositol prior to IVF treatment may favor the control of ovulation induction.

Pretreatment in Patients Non-PCOS Undergoing IVF

The literature on the pre-treatment in patients not - PCOS is not so extensive compared to the literature of pre-treatment in PCOS patients. Has been observed[28] that higher concentration of MI and E2 in human follicular fluid appear to play a role in follicular maturity and can be considered a reliable marker of good quality oocytes; the mean concentration of MI was found higher in follicular fluid containing oocytes that developped into embryos with good morphology. Again same authors[29] suggest that MI may affect meiotic progression of mouse GV oocytes possibly by enhancing the intracellular Ca2+ oscillations. Supplementation of MI in culture medium may be useful for human oocyte maturation. We[30] also studied the effect of pretreatment with 4000 mg/die of inositol and 400μg of folic acid in normoovulatory patients aged <40 years and with basal FSH <10 mUI/ml undergoing multiple follicular stimulation after dowregulation with triptorelin acetate for IVF. Our findings suggested that the addition of myo-inositol to folic acid in non PCOS-patients undergoing multiple follicular stimulation for in-vitro fertilization may reduce the numbers of mature oocytes and the dosage of rFSH required to achieve follicular maturity whilst maintaining clinical pregnancy rate. Further, a trend in favor of increased incidence of implantation in the group pretreated with myo-inositol was apparent in this study. More recently[31] were compared 38 patients pretreated with MI (4 g) + folic acid (FA) (400 μg) for the previous 3 months before the enrollment day with 38 patients assuming FA (400 μg) alone; in this study patients pretreated with MI needed a total rec-FSH units significantly lower to reach follicular maturation and M2 oocytes rate was significantly higer suggesting a MI role in improving ovarian response to gonadotropins.

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