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Communication

PCOS and Assisted Reproduction Technique: Role and Relevance of Inositols

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Abstract: Polycystic ovary syndrome is an endocrine disorder often characterized by insulin resistance and hyperinsulinemia, especially in overweight/obese women. Among insulin sensitizers, the positive role of inositols has been increasingly established in recent years. The action of inositols not only concerns the metabolic parameters of these patients, but also the hormonal profile, resulting in beneficial effects on ovarian function. For this reason, many studies have tried to recognize their role in PCOS infertile women who underwent in vitro fertilization (IVF) procedures.

Keywords: polycystic ovary syndrome; PCOS; inositols; ART; myo-inositol; D-chiro-inositol

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1. Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder which, according to some authors, can involve up to 25% of women of reproductive age [1]. Although it is not part of the Rotterdam diagnostic criteria drawn up in 2003 [2], insulin resistance (IR) and hyperinsulinemia are often observed in PCOS patients, compromising not only the hormonal aspect but also the metabolic one.

The diagnostic criteria currently in use includes at least two of these three elements: oligo or anovulation, clinical and/or biochemical hyperandrogenism, and a polycystic morphology of the ovaries [2].

In recent years, more and more studies have focused their attention and research on the metabolic modification of this pathology. Impaired glucose tolerance, insulin resistance, and the consequent hyperinsulinemia, are estimated to affect 40–50% of PCOS patients [3], mostly in overweight or obese women.

Especially in normal-weight patients, a strong genetic/familial predisposition of diabetes was also hypothesized to explain the mechanism underlying insulin resistance (IR) [4–6].

In fact, familial diabetes triggers an impaired expression/function of the post-receptor signaling of insulin, as demonstrated by several studies, independent of body weight [7,8].

In our recent work [9], we explained how hyperandrogenism, which we often find in these patients, can further negatively affect glucose metabolism, reducing peripheral and hepatic insulin action [10]. If PCOS women with central obesity are compared with those of normal weight, a higher percentage of free androgen levels and IR were highlighted in the first group [11]. Furthermore, the cells were stimulated by insulin and LH to produce and secrete androgens and hyperglycemia inhibits the hepatic synthesis of sex hormone-binding globulin (SHBG), whose reduction causes an increase in the concentration of circulating free androgens [12,13].

Consequently, the excessive production of androgens is the basis of impaired follicular development. Analyzing the hormonal profile of patients with PCOS, it is possible to highlight elevated concentrations of androgens, an increase in luteinizing hormone (LH) and an increase in estrogen levels produced by the extra glandular conversion from androgens, as well as a decrease in the values of SHBG [9,11,14].

It is evident that infertility often occurs in these patients due to the combination of both chronic anovulation and hyperandrogenism [15], which are the two classic features that trigger the request and the need of gynecological and endocrinological help.

The mechanism underlying PCOS has not yet been fully clarified; however, several authors suggested that adequate treatment of insulin resistance in PCOS infertile patients could improve the response of the ovary to endogenous gonadotropins which appear to be worsened by IR. This mechanism alone may be able to restore normal menstrual cycle and ovulation for those patients with PCOS [16–19].

2. Therapeutic Approach to Insulin Resistance

Several insulin-sensitizing drugs have been proposed to treat IR [20], such as metformin, pioglitazone, and troglitazone, in order to reduce serum androgens and improve ovulation [15,17–19], alongside making lifestyle changes. Body weight reduction in overweight or obese patients is essential to achieve normal ovulatory function [9,21].

Among them, metformin has been the most widely used drug for many years. However, if used at high dosages, as is often necessary based on the patient's metabolic impairment, it can produce many gastrointestinal side effects [5,22].

For this reason, in the last two decades, many authors have begun to introduce inositols among the therapeutic options of these patients. Inositols can positively affect several aspects of PCOS, acting first on insulin resistance and on other metabolic aspects of these patients, such as a reduction of total and free testosterone, lowering of blood pressure, and a better control of blood glycaemia [9].

Among the various forms of known inositols, the two clinically active isoforms in our bodies are myo-inositol (MYO) and D-chiro-inositol (DCI) [23–25].

In their conjugated form, inositols are membrane components and they take part in a great variety of functions, including cell growth and survival, and development and function of peripheral nerves and reproduction. Phosphatidylinositol is the precursor of phosphatidylinositol phosphate and phosphatidylinositol diphosphate (PIP2), which, upon hydrolysis by phospholipase C (PLC), gives inositol 1,4,5 trisphosphate; the latter acts as a second messenger of membrane receptors coupled to PLC, being involved in the signaling mechanism of many autacoids, hormones, and neurotransmitters [26].

MYO and DCI both play a fundamental role within the cell to ensure a constant change in the glucose concentrations inside the cytosol, but with different actions: MYO determines the upload of glucose into the cell, while it is the DCI that allows it to be stored in glycogen or used [27].

In fact, the coupling of the functions of both these inositols determines on one hand, through MYO the correct upload of glucose from the extracellular space into the cytoplasma; on the other hand, through DCI, it determines the improvement of the glucose storage as glycogen and the oxidative use of glucose to produce energy at the mitochondrion level [27].

Such events permit a perfect gradient of concentration of glucose from the extracellular space to the cytoplasm. It is clear that both MYO and DCI are involved not only in the insulin-signaling pathway but also in glucose use, and whatever impairs the equilibrium between MYO and DCI, impairs the ability to use glucose, thus triggering insulin resistance [27,28].

DCI is a product of the epimerization of the C1 hydroxyl group of MYO by an insulin-dependent enzyme, NAD/NADH epimerase [29]. In PCOS patients, like in type 2 diabetes patients, the activity of epimerase is reduced in the way that the concentration of MI is increased. Due to that pathway, the concentration of DCI results decreased, as found in urines [30].

The reduction of DCI may result in decreased availability of inositolphosphoglycan (IPG), a second messenger of insulin, thus contributing to the insulin resistance. Additionally, oxidative stress was reported to be increased in women with PCOS and to contribute to the insulin resistance state [31].

3. Inositol and IVF Treatments

In recent years, the role of inositol in fertility has been increasingly highlighted and studied, especially for women with PCOS who require assisted reproductive technology (ART).

In this context, the predominant role is certainly recognized by the MYO.

MYO increases permeability of the cell membrane to glucose and seems to play a crucial role at the ovarian level [32] and in the reproductive organs, acting not only on the development of gametes, but also positively on oocyte maturation and quality, fertilization, and early embryonic development [33–35]. MYO administration seems to improve reproductive parameters, throughout the interaction between insulin, thyroid-stimulating hormone (TSH), LH, follicle-stimulating hormone (FSH), and ovarian androgen production [25,26,36–38], with a beneficial action on the ovulation frequency [15,16,39–42].

MYO takes part in many signal pathways, such as the pathways of insulin and gonadotropins. It is the second messenger of FSH and LH, so it acts positively also on follicle maturation and reducing hyperinsulinemia, which worsens menstrual regularity and reduces fertility [43–46].

Specifically analyzing the context of ART procedures, Chiu et al. in 2016 have reported that high concentrations of MYO positively correlate with mature and high-quality oocytes and high-quality embryos during IVF treatments [47,48].

In PCOS women undergoing in vitro fertilization, MYO is effective in reducing the length of ovarian stimulation [49] and the amount of r-FSH used during controlled ovarian hyperstimulation for IVF-ET (fertilization in vitro embryo-transfer) and ICSI (intracytoplasmic sperm injection) [4].

Supplementation with MYO can promote meiotic progression into fertilization-competent eggs, while depletion of MYO may lead to the interruption of oocyte maturation [50,51].

It has been demonstrated that the proportion of fertilized oocytes, the number of two-cell stage embryos developed, and the percentage of normality of the post-implantation embryos were significantly higher when germinal vesicles were cultured in a maturation medium containing MYO [52].

Although the beneficial role of MYO is increasingly clear, the literature has often confused its use in IVF, mainly with regard to dosages. For this reason, in 2021, a review wanted to clarify the matter [53]. They summed up the main randomized studies on the effect of MYO, alone or with DCI, in PCOS women that underwent IVF. Among the main works analyzed and taken into consideration by the French group, there was a randomized controlled trial (RCT) of Unfer of 2011. Unfer et al. [54] analyzed IVF outcomes in 84 euglycemic women starting 2 months before controlled ovarian hyperstimulation (COH) for ICSI; 43 patients received MYO 4 g/day therapy, while 41 women received DCI 1.2 g/day therapy. Although there were no differences between the two groups in the number of oocytes retrieved, the patients who had taken MYO showed a significant increase in the number of mature oocytes and good quality embryos, showing the positive role of MYO in PCOS women without hyperinsulinism.

In the same year, Ciotta et al. [55] published another RCT with a smaller sample of patients, which differed slightly from the previously listed results. They compared 17 women who were given MYO 4 g/day plus folic acid to 17 women who took folic acid alone in the 3 months prior to IVF. The results of this study confirmed that MYO resulted in an improvement in the quality of the embryos, but also demonstrated a statistically significant increase in the number of oocytes retrieved.

The same dosages of MYO were used in a further RCT in 2016, alone or in combination with melatonin. In this study, the control group consisted of 195 PCOS women who took only folic acid, who were compared with 331 PCOS women who also took MYO 4 gr/day, with or without melatonin. This study gave us further confirmation of the previous results, i.e., it shows us an increase in the number of oocytes recovered and the number of good quality embryos obtained in the study group. There is also a reduction in the dose of

FSH used during COH. According to the authors, the greatest positive effect was given synergistically by MYO and melatonin [56].

Previously, the positive effect of MYO on the total dose of FSH used during COH in PCOS patients undergoing ART had already been highlighted. In this study, MYO was administered at a dosage of 2 g/day for 12 weeks. Comparing these patients to those of the control group, it was shown that in the MYO treated group, the duration of stimulation was shorter ($p = 0.002$) and the FSH dosage used was lower in the MYO treated group ($p = 0.002$) [4].

The need for reduced FSH dosages as well as reduced concentrations of estradiol and fewer cancelled cycles also allows us to understand how the use of MYO in PCOS patients undergoing IVF can substantially reduce the risk of ovarian hyperstimulation syndrome (OHSS) and, therefore, complications [4,16,57].

At the end of the analysis carried out, Merviel et al. [53] concluded that the use of MYO could be useful in patients with PCOS who underwent ART, with a particular benefit on oocyte and embryo quality; they recommended the dosage of 4 g per day, starting 3 months before stimulation.

Like them, other authors also focused on the effect of inositol on embryos and oocytes. Gupta et al. [58] previously published a review in which they analyzed nine studies from 2009 to 2018, to investigate the role of MYO supplementation and its possible correlation with the quality of oocytes/embryos. They analyzed the number of metaphase II oocytes and the number of morphologically grade-one embryos to evaluate the aforementioned outcomes. However, the studies analyzed showed non-homogeneous or conflicting results. Regidor et al., for example, demonstrated how MYO determined an increase in the number of metaphase II oocytes retrieved and in the number of grade I embryos, but it was not statistically significant [58,59].

Papaleo et al. instead showed that in women with PCOS who underwent ICSI, taking MYO (2 g twice a day) resulted in a significant reduction of the mean number of germinal vesicles and degenerated oocytes (1.0 ± 0.9 vs. 1.6 ± 1.0), although there were no differences in the number of oocytes retrieved by comparing the study group to the control [57].

In another prospective randomized study from 2016, 14 PCOS patients who took 4 g of MYO plus folic acid were compared with 15 PCOS patients who did not take this therapy. All of these patients underwent IVF procedures 2 months later. The authors highlighted a statistically significant increase in the number of fertilized oocytes in the study group ($p < 0.05$), but a non-statistically significant increase in the number of metaphase II and I oocytes retrieved, in relation to the total amount of oocytes ($p > 0.05$). More embryos of grade I quality were observed in the MYO group ($p < 0.05$) [60]. On the contrary, Mendoza published a systematic review and meta-analysis of randomized controlled trials, in which he stressed that MYO supplementation in women undergoing ICSI was not sufficient for improving oocyte quality and embryo quality [61].

Although most of the results are strongly encouraging towards the use of MYO and its advantages within IVF in PCOS patients, the authors ultimately conclude that to make a final definitive judgment about it, a large multicentric RCT is required [58].

Similar conclusions were published in a review by Garg et al., in which they summarized the main studies that analyzed ART outcomes in PCOS women with/without inositol intake. This time, the evidence supported the use of MYO, confirming its positive role during IVF/ICSI, thanks to an improvement in the number of mature oocytes retrieved, oocyte quality, and embryo quality. However, at the end of their analysis, the same authors expressed a negative opinion on the role of D-chiro-inositol, which seemed to have detrimental effects on the ovary [12].

The role of DCI is still debated, both in regard to its possible association with MYO in patients undergoing IVF and its dosage. Numerous authors have tried to identify its role. In 2014, Piomboni et al. [62] used a study sample of 68 patients diagnosed with PCOS, who were randomly divided into three groups: a group treated with DCI (500 mg bid), a group treated with Metformin, and a group that did not take any therapy. The patients

took 3 months of therapy, at the end of which they underwent an ovarian stimulation protocol. A significantly higher number of top-quality oocytes were obtained from women treated with DCI or metformin (in comparison with the untreated group). The authors concluded by indicating how DCI could improve the outcomes of these patients, thanks to its positive role both on reduction of oxidative stress on follicular fluid and on increase of oocyte quality.

More recently, Mendoza et al. [63] wanted to investigate the effects of an association of DCI and MYO in non-obese PCOS patients who underwent ICSI. In the 3 months prior to controlled ovarian stimulation, 30 patients in the study group took MYO + DCI 3.6:1 (550 mg of MYO + 150 mg of DCI, twice daily), while another 30 patients in the control group took MYO + DCI 40:1 (550 mg of MYO + 13.8 mg of DCI, twice daily). Among the results, the authors demonstrated how there were no statistically significant differences in the two groups regarding the number of MII oocytes and percentage of good-quality embryos, however the high-dosage group showed a significantly higher pregnancy rate than controls. Other studies have instead concluded that high doses of DCI could determine some toxicity, with harmful effects on the ovary [16]. It is therefore evident that the role of the DCI is still debated, and more extensive work is needed.

4. Conclusions

It appears clear that PCOS is a rather complicated endocrinological disease that is extremely dependent on the androgen production which is dependent on genetic predisposition to an increase in insulin levels. The presence of inositols inside the cells of any compartment is at the basis of the function of any organ. Inositol appears to have beneficial effects on ovarian function and response to assisted reproduction technique in women with PCOS.

Therapy with inositol in PCOS patients reduced FSH dosages utilized as well as the levels of estradiol. Furthermore, we can see a reduced cancellation of cycles and consequently a decrease in OHSS. Biologically, inositol therapy increases the number of mature oocytes retrieved, oocyte quality, and embryo quality, as well as of pregnancy rate.

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