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EDITORIAL

Inositols: from physiology to rational therapy in gynecological clinical practice

Vittorio Unfer[a], Beatrice Orrù[b] and Giovanni Monastra[c]

[a]Department of Medical Sciences, IPUS – Institute of Higher Education, Chiasso, Switzerland; [b]LO.LI. Pharma, Medical Department, Rome, Italy; [c]Systems Biology Group, Department of Experimental Medicine, University la Sapienza, Rome, Italy

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1. Introduction

It is now a common understanding that to define a rationale for an effective therapy, an in-depth knowledge of physiology as well as pathology related to the specific issue is critical. This is the case for inositol supplementation.

Inositols belong to the polyols family and form nine different stereoisomers. These molecules – mainly the stereoisomer called myo-inositol (myo-Ins) – have gained momentum during the last decades as novel promising treatment for a wide range of pathological conditions namely gynecological diseases, insulin resistance, respiratory distress syndrome in newborns, psychiatric illness, and even cancer [1]. The purpose of this editorial is meant to guide the reader through the study of the physiological role exerted by inositols, which enhances the rational therapeutic use of these molecules mainly focusing on gynecological practice.

2. Physiological role of inositol in the glycemic homeostasis

Myo-Ins and D-chiro-Inositol (D-chiro-Ins), which is another type of stereoisomers, exert a key role in controlling glucose homeostasis. Myo-Ins can be converted into D-chiro-Ins by the epimerase, which is an enzyme stimulated by insulin. Ostensibly a reduction in epimerization is a crucial factor in the pathogenesis of polycystic ovary syndrome (PCOS). Myo-Ins and D-chiro-Ins, intracellularly incorporated into inositolphosphoglycans (IPGs), play the pivotal role as second messengers of insulin. Nevertheless, their physiological function is different: D-chiro-inositol-containing IPGs (D-chiro-Ins-IPGs) mediate glycogen synthesis, while myo-inositol-containing IPGs (myo-Ins-IPGs) mediate glucose uptake at the cellular level. In fact, cells responsible for glycogen storage (such as liver, muscles, and fat cells) contain high levels of D-chiro-Ins, whereas elevated concentrations of myo-Ins are found in brain and heart cells, as they require a notable consumption of glucose. The intracellular ratio between myo-Ins and D-chiro-Ins (myo-Ins/D-chiro-Ins) seems to be tissue specific (for instance, in the ovary, the myo-Ins/D-chiro-Ins ratio is 100:1) [2]. Clinical observations have shown that the concentration of D-chiro-Ins-IPGs in muscle cells and D-chiro-Ins in urine of diabetic patients decreases [3]. On the contrary, the amount of D-chiro-Ins significantly increases in the follicular fluid of insulin-resistant patients [3]. This discrepancy depends on the fact that insulin resistance does not affect all tissues; indeed, ovaries and testicles never become insulin resistant. Insulin resistance induces a compensatory hyperinsulinemia which stimulates the epimerase, therefore increasing D-chiro-Ins concentration in either ovaries or testicles. The increased conversion to D-chiro-Ins leads to a drastic reduction of myo-Ins intracellular levels. It explains the altered function in spermatogenesis and ovulation occurring in hyperinsulinemic patients.

3. PCOS and D-chiro-Ins supplementation

PCOS is associated with metabolic syndrome. In PCOS women, an impaired release of D-chiro-Ins-IPGs may contribute to insulin resistance. The effectiveness of D-chiro-Ins in improving insulin sensitivity through the enhanced release of D-chiro-Ins-IPG is still to be established. Nevertheless, it has been shown that in such patients, the increased release of D-chiro-Ins-IPGs is significantly linked with improved insulin sensitivity, highlighting that D-chiro-Ins-IPG mediators can be a suitable target for a therapeutic intervention in this syndrome [4]. To determine that D-chiro-Ins administration shows positive effects on PCOS by ameliorating insulin resistance, a randomized, double-blind controlled trial was conducted on obese women affected by this disorder [5]. The patients received D-chiro-Ins or placebo for 6–8 weeks. The results demonstrated that D-chiro-Ins improved insulin activity in these subjects, thereby recovering the ovulatory function and decreasing parameters such as serum androgen concentration, blood pressure, and plasma triglycerides. There was a significantly higher ovulation ratio (87%) in women affected by PCOS treated with D-chiro-Ins compared to placebo, who showed only a slight improvement (27%). D-chiro-Ins supplementation was associated with a decrease of serum testosterone and an increase of serum sex hormone-binding globulin (SHBG) [5]. These results are similar to those reported previously in PCOS obese women treated with D-chiro-Ins [4,5]. Remarkably, 60% of women in D-chiro-Ins group ovulated compared to 20% of women in placebo. Overall, these results support the idea that insulin resistance is a feature of PCOS in lean women and plays a key role in the pathogenesis of this syndrome. Notwithstanding,

CONTACT Vittorio Unfer vunfer@gmail.com

D-chiro-Ins mechanism of action has not been utterly outlined yet, the current findings support the hypothesis that insulin resistance in lean women with PCOS may be related, in part, to a lack of D-chiro-Ins-IPGs. This anomaly may be caused by a decrease in D-chiro-Ins production or an upregulation of its metabolism. Interestingly, it was shown that supplementation of D-chiro-Ins is effective in restoring the insulin sensitivity and hormone profile, particularly in hyperinsulinemic PCOS subjects with a family history of diabetes [6].

4. Warning: D-chiro-Ins dose–response

Recently, the role played by D-chiro-Ins in the ovary was further investigated. Different doses of D-chiro-Ins were administered in euglycemic women with PCOS revealing that high concentrations of D-chiro-Ins negatively affect the quality of oocytes and the ovarian response to follicle-stimulating hormone (FSH) in non obese and non–insulin-resistant PCOS women [7]. Interestingly, this effect was observed by Cheang et al. using the same D-chiro-Ins dosage [4]. Overall, patients seeking for pregnancy should not be treated with D-chiro-Ins due to its negative effect on ovaries, while women not interested in pregnancy might get a benefit from a proper dosage of D-chiro-Ins, especially if they have a familial predisposition to diabetes.

5. Myo-inositol and infertility

Myo-Ins deficiency in women with PCOS is associated with poor oocyte quality and altered folliculogenesis. Conversely, a number of studies showed that significantly higher concentrations of myo-Ins in the follicular fluid were correlated with good-quality oocytes, thereby promoting the development of equally high-quality embryos, in subfertile patients. Positive and significant correlations between myo-Ins concentrations and the segmentation of fertilized ovules were found. Furthermore, myo-Ins administration in women undergoing *in vitro* fertilization reduces the amount of recombinant follicle stimulating hormone (r-FSH) and the stimulation days and improves the oocyte and embryo quality as well as the implantation rate [8]. A number of studies have demonstrated that in the majority of infertile PCOS patients, oral supplementation of myo-Ins restores spontaneous ovulation and menstrual cycles and increases progesterone secretion in the luteal phase [9]. These findings are in line with other trials where different insulin-sensitizing agents were evaluated in monotherapy or in combination with clomiphene citrate; this suggests a positive effect exerted by myo-Ins on spontaneous ovarian activity. Besides, it was illustrated that myo-Ins therapy is able to reduce both total and free testosterone levels in serum as already seen with D-chiro-Ins. The effect of myo-Ins was evaluated also in 92 women with oligomenorrhea, amenorrhea, or PCOS. Patients were treated with myo-Ins combined with folic acid or folic acid alone as control. The results showed a significant increase of ovulation rate in the study group compared to control [9].

6. The effect of insulin on inositols

Insulin plays an important role in the pathogenesis of PCOS, both directly and indirectly. In fact, insulin exerts a direct action in the ovary, where it induces the synthesis of androgens [1], in a synergistic action with the luteinizing hormone (LH) on theca cells [10]. Insulin determines the relationship between its two messengers, stimulating the epimerase enzyme. Furthermore, insulin reduces circulating SHBG by acting indirectly in the liver and increases free testosterone. The deep relationship between hyperinsulinemia and PCOS induces to consider this syndrome more a metabolic problem than reproductive. The improved insulin sensitivity in women with PCOS, by means of insulin-sensitizing drugs, gives a better ovarian function and a reduction of androgen concentration in serum. PCOS patients with hyperinsulinemia are likely to have a greater epimerization of myo-Ins to D-chiro-Ins in the ovaries. This could cause an increase in D-chiro-Ins/myo-Ins ratio (i.e. an overproduction of D-chiro-Ins), with a consequent myo-Ins deficiency in the ovary. According to Larner's data, cells with high insulin sensitivity increase the epimerase activity in transforming myo-Ins to D-chiro-Ins and decreasing myo-Ins/D-chiro-Ins ratio [11]. Conversely, all previous studies had shown a reduced epimerase activity and an increase in myo-Ins/D-chiro-Ins ratio in presence of insulin resistance. Moreover, it has been shown that oxidative stress might lead to a proinflammatory state, which in turn induces insulin resistance and hyperandrogenism in PCOS women. Indeed, in PCOS patients, mononuclear cells release reactive oxygen species in response to increased hyperglycemia [12]. Therefore, the putative antioxidant activity of myo-Ins finds a further explanation in PCOS treatment.

7. Myo-Ins/D-chiro-Ins ratio

The recent 'International Consensus Conference on myo-Ins and D-chiro-Ins in Obstetrics and Gynecology' (2013) [13] has highlighted that both myo-Ins and D-chiro-Ins are critical molecules in the treatment of PCOS. However, for a proper treatment of PCOS patients, the correct ratio between these two isomers had to be identified. A recent study emphasized the difference in the concentration of myo-Ins and D-chiro-Ins in the follicular fluid of 20 normal women and 20 PCOS women. The ratio between myo-Ins and D-chiro-Ins resulted to be 100:1 in normal women, and only 0.2:1 in PCOS women, who also had a significantly higher levels of LH and elevated hyperinsulinemia and insulin resistance [2]. This is the first study that analyzes the imbalance between myo-Ins and D-chiro-Ins in the ovary of patients affected by PCOS. It highlights the significance in maintaining the physiological levels of these two stereoisomers to restore ovarian function. Likewise, Nordio and Proietti concluded that the combined supplementation of myo-Ins and D-chiro-Ins (40:1) should be considered as the first approach in overweight PCOS patients, as it is able to normalize the metabolism and reduce the clinical alterations of PCOS, consequently decreasing the risk of metabolic syndrome [14].

8. Expert opinion

Since inositol has been isolated, several breakthroughs have been made in regard to this molecule, from the identification as calcium and insulin second messenger to its use in clinical practice for reproduction and PCOS.

Overall, the studies reported here give prominence to myo-Ins as a therapeutic approach of great interest. Its efficacy in treating various aspects of PCOS, as well as gestational diabetes and metabolic syndrome, is emphasized by its extreme tolerability, lacking those appreciable side effects recorded when common drugs – like metformin and thiazolidinediones – are used in treating PCOS. The effectiveness of myo-Ins and metformin was evaluated, as monotherapy or in combination with r-FSH, for treatment of menstrual irregularities, chronic anovulation, and female infertility in PCOS patients. As a result, myo-Ins and metformin were considered as a first-line treatment in restoring the normal menstrual cycles in most PCOS patients. However, a more efficient effect of myo-Ins compared to metformin was evidenced [9].

A relevant milestone about myo-Ins was achieved in 2007 demonstrating that myo-Ins supplementation could restore spontaneous ovarian activity and consequently fertility in patients with PCOS [9]. Following the same fashion, recent studies showed the positive effect on hormonal functions and on insulin sensitivity in target tissues of PCOS subjects [15]. Myo-Ins seems to play a crucial role in oocytes, representing about 99% of inositol intracellular pool [2]. Thus, myo-Ins may be considered an important part of the follicular microenvironment and a valuable marker of oocyte quality, playing a key role in both nuclear and cytoplasmic oocyte development.

In addition, D-chiro-Ins alone, as a putative insulin-sensitizing drug, has shown to ameliorate metabolic abnormalities associated with insulin resistance in PCOS patients, improving glucose tolerance and reducing circulating insulin and serum androgen concentrations. However, D-chiro-Ins supplementation at high daily dosage has shown a negative effect on oocyte quality and ovarian response [7]. Administering the two stereoisomers combined proved to be the most acceptable solution in establishing an efficient therapy for PCOS.

The studies conducted so far have identified diverse dosages, aimed at different therapeutic targets and innovative formulations, providing the right physiological ratio of both molecules. Supplementation of both molecules in a physiological ratio 40:1 appears to be safe and effective in restoring metabolic balance, altered in PCOS women and preventing the development of pathologies like gestational diabetes.

However, there is a need for future properly controlled studies on larger cohorts of PCOS patients, with a higher statistical power, which would (1) clarify more accurately posttreatment outcomes with the diverse inositol isoforms, (2) increase even more the optimal therapeutic strategies tailored to different personalized treatments, and (3) evaluate the variability of the long-term outcomes on the basis of PCOS phenotypic parameters.

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Declaration of interest

V Unfer and B Orrù are employees at LO.LI.Pharma, Rome, Italy. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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