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Evidence-Based and Patient-Oriented Inositol Treatment in Polycystic Ovary Syndrome: Changing the Perspective of the Disease

Antonio Simone Laganà,[1,*] Paola Rossetti,[2] Fabrizio Sapia,[3] Benito Chiofalo,[1] Massimo Buscema,[2] Gaetano Valenti,[3] Agnese Maria Chiara Rapisarda,[3] and Salvatore Giovanni Vitale[1]

[1]Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy
[2]Unit of Diabetology and Endocrino-Metabolic Diseases, Hospital for Emergency Cannizzaro, Catania, Italy
[3]Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy

[*]*Corresponding author*: Antonio Simone Laganà, Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy. Tel: +39-0902212183, Fax: +39-0902937083, E-mail: antlagana@unime.it

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1. The Rationale of Inositol Therapy in Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS)'s rate is about 6% to10% among the reproductive aged women; it is characterized by menstrual cycle irregularity with oligo-anovulation, hyperandrogenism, insulin resistance, and compensatory hyperinsulinemia. Despite the fact that the last two elements are present in a large percentage of PCOS women, they are not mandatory for the diagnosis; in order to explain the pathogenesis in these patients, it was supposed that ovarian theca cells got higher insulin sensitivity probably related to the mechanism of intracellular signalling transduction (1). Corroborating this view, it was previously demonstrated that diazoxid, which has the well-known effect of decreasing insulin levels, reduced hyperandrogenism in lean women affected by PCOS, even in the cases of normal insulin level and insulin sensitivity (2). Based on the detrimental role of insulin resistance, several insulin sensitizer drugs have been used to ameliorate PCOS symptoms and signs. Although metformin has represented the landmark of PCOS therapy in the recent past, to date several studies have tested the efficacy of Inositols, a carbocyclic polyols. Two stereoisomers, in particular Myo-inositol (MI) and D-Dhiro-inositol (DCI) showed a clinical efficacy and safety during PCOS. MI is converted in DCI by epimerase, an enzyme regulated also by insulin action. In the form of inositol-phosphoglycans (IPGs), they are involved in a non-classical insulin signalling cascade: insulin receptor is coupled by G-protein which can activate phospholipase, allowing the release of second messengers (DCI-glycan), which is able to stimulate pyruvate dehydrogenase and glycogen synthase activities, the enzyme involved in the oxidative and the non-oxidative glucose metabolism (3). On one hand, MI-IPG is able to inhibit cyclic adenosine monophosphate (cAMP) kinase and adenylyl cyclase, both involved in free fatty acid metabolism. On the other hand, DCI-IPG play a pivotal role during the binding of insulin to its receptor on cell membrane where it stimulates IPG release and starts signalling cascade. In addition, Inositols are incorporated in membrane phospholipids as phosphoinositides. Phosphatidylinositol 4, 5 bisphosphate (PtdIns-4, 5P) and phosphatidylinositol 4P (PtdIns-4P), in particular, are involved in the regulation of the cytoskeleton structure and in the regulation of cellular motility, which account also the beneficial effects of Inositol administration on sperm parameters. PtdIns-4, 5P plays a key role in controlling calcium-mediated intracellular signalling which is mandatory to address the oocytes maturation and fecundation (4).

2. Overview of Clinical Studies

In these last twenty years Inositols have been studied as a helpful alternative to metformin. As stated before, the insulin-like actions of nutritional inositol are due to the production of inositol glycan secondary messengers which contain MI or DCI. Recently, our group have tested the effects of oral administration of 1 gr of DCI + 400 mcg of folic acid per day in a large cohort of PCOS women (5). After 6 months of treatment, we found a significant reduction of prolactin, Δ-4-Androstenedione, Ferriman-Gallwey score, LH, systolic blood pressure, free Testosterone, LH/FSH ratio, HOMA Index, and total testosterone; in addition, we found a significant increase of Glycemia/IRI ratio and Sex hormone binding globulin. Finally, we found significant post-treatment menstrual cycle regularization. Similar results were found in an accurate systematic review of ran-

domized controlled trials (6) which tested MI in PCOS population. In addition, a recent randomized trial showed that both MI and DCI improved ovarian function and metabolic profile in patients affected by PCOS, although DCI showed the most marked effect on hyperandrogenism, MI reduced insulin resistance more effectively (7). Considering the accumulating evidence on this topic, several studies investigated the effects of combined DCI and MI, demonstrating a better and faster re-addressing of hormonal and metabolic parameters in PCOS population, maintaining the widely known safety profile (1). Although the last Cochrane systematic review about the topic does not offer a robust recommendation about the best treatment for PCOS among metformin, rosiglitazone, pioglitazone and DCI (8), a recent trial did not find any significant difference between metformin and MI in lowering BMI, ameliorating insulin sensitivity, and improving menstrual cycle (9). Nevertheless, in the evaluation of the available evidence, we should consider that Inositol administration is more effective in obese patients with high fasting insulin plasma levels (10).

Last but not least, both isoforms of Inositol proved to be effective, also, in combination with other nutraceuticals which enhance their insulin sensitizing action; in particular, considering the close connection between oxidative stress and impaired ovarian follicular maturation, the combination of MI and Melatonin significantly improve the quality of oocytes and the quality of embryos (3).

3. Conclusion

Since many studies showed that both MI and DCI treatment were effective to improve PCOS symptoms and signs, these two insulin-sensitizers gained increasing popularity among gynecologists and endocrinologists. Complicit of this boom of prescriptions, it should be not underestimated that the favorable safety profile of the two stereoisomers allows their administration even in pregnancy in order to prevent gestational diabetes mellitus. In addition, MI and DCI showed to be effective both in obese and lean PCOS women, suggesting that the typical insulin resistance of this kind of patients should be considered pivotal not only in the case of high BMI. Indeed, in our opinion, PCOS can be considered as the result of concurrent and inter-related endocrine alterations; recent data suggest that hyperinsulinemia and insulin resistance have paramount importance in the development of hyperandrogenism, which in turn causes anovulation. Furthermore, LH works in combination with hyperinsulinemia to increase androgen production by adrenal and theca cells. Based on these elements, it is not surprising that MI and DCI achieved excellent results on metabolic and hormonal parameters in PCOS women. In addition, re-addressing them to the homeostatic levels allows an improvement of ovulation, oocyte quality, and pregnancy rate.

Despite the promising results, we take the opportunity to solicit additional studies on larger cohorts and adequate statistical power in order to establish the most suitable therapeutic strategies based on the patient's clinical condition; in particular, future research should be aimed to compare Inositols to the other insulin sensitizers (rosiglitazone, pioglitazone) and to test new combinations of them on different PCOS phenotypes.

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