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Four Years of EGOI: Between Science and Clinical Practice on Inositols. Meeting Report ISGE 2024 – EGOI-PCOS Session

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Introduction

Inositol has increasingly come under the spotlight as research into its biological function and applications has continued to increase. Currently, inositol is utilized as an insulin sensitizer in a similar manner to metformin in the field of polycystic ovary syndrome (PCOS) and is also known to be involved in steroidogenesis [1]. Consequently, it was mentioned within the recently published international clinical guidelines on PCOS albeit still as an experimental therapy [2].

These guidelines were discussed at length, alongside other major topics at the ISGE Gynecological Endocrinology 21st world conference that was held in Florence Italy between the 8th and 11th May. During the conference, the Expert Group on Inositol in Basic and Clinical Research and on PCOS (EGOI-PCOS) hosted a session to discuss recent progress in inositol research within the field of PCOS and to celebrate 4 years since the founding of the EGOI. Established with the mission of exploring the key physiological functions and clinical applications of inositol across a variety of disease areas, the EGOI has expanded to include international experts from various disciplines such as gynecology and endocrinology. In the last year, PCOS has emerged to be the primary focus of the group, particularly the metabolic aspect of this condition, leading to the incorporation of the syndrome within the name of the society.

Herein, we describe the talks given during the EGOI-PCOS session with the aim to stimulate further research into the applications of myo-inositol. Finally, we would like to express our deepest gratitude to all the session's participants, whose collaboration and engagement helped foster a dynamic and enlightening meeting.

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Advances with Inositol in PCOS

PCOS represents the most common metabolic endocrinological disorder in women, affecting 5–15% of women worldwide. In 2003, the Rotterdam Criteria laid out a series of diagnostic criteria for PCOS, which defined PCOS as a condition presenting two of the following: biochemical and/or hyperandrogenism, oligo-anovulation, and polycystic ovarian morphology. The etiology of PCOS is multifactorial and metabolic alterations, such as insulin resistance (IR), represent one of the most important drivers of the condition, with increased insulin levels directly and indirectly increasing androgen levels. This is reflected in the prevalence of IR in both lean and obese PCOS patients, which is 40% and 80%, respectively. In this context, insulin sensitizers such as metformin and inositol have demonstrated success in treating PCOS. Therapeutically inositol is represented by two stereoisomers, namely myo-inositol and D-chiro-inositol, which, respectively, encourage glucose transport into the cell and facilitate glycogen storage. Moreover, the ratio of these two stereoisomers is perturbed within the ovaries of PCOS patients, resulting in a higher concentration of D-chiro-inositol [3], which also inhibits the genetic expression of aromatase and leads to higher testosterone levels. The supplementation of myo-inositol alone or in combination with D-chiro-inositol has been observed to restore homeostasis between these stereoisomers, thus improving hormonal, reproductive, and metabolic alterations commonly seen in hyperandrogenic PCOS. While the most recent international guidelines still classified inositol as an experimental therapy, in numerous RCTs metformin and myo-inositol were shown to be equally efficacious in treating PCOS, with myo-inositol demonstrating less gastrointestinal adverse effects [4]. Myo-inositol may have application in the field of reproductive medicine as it has been shown to reduce the number of vials of rFSH required for performing ovarian stimulation in PCOS patients, reducing also the risk of ovarian hyperstimulation syndrome [5]. Furthermore, in separate studies, oocyte quality was improved in women taking myo-inositol while undergoing assisted reproductive procedures [6]. In total, inositols are generally safe and well-tolerated with an excellent safety profile; however, further studies (larger scale and multi-centered RCTs) are required to fully establish their clinical potential and to optimize treatment protocols.

Comparing the Efficacy of Myo-Inositol plus α-Lactalbumin versus Myo-Inositol Alone on Reproductive and Metabolic Disturbances of PCOS

"All diseases start in the gut" first theorized Hippocrates, this thought has continued into the modern day with the role that microbiota and the microbiome play in current medical practices. Of interest to the fields of gynecology and endocrinology is gut microbiota as it plays a role in numerous conditions including obesity, diabetes, insulin resistance, and PCOS. In this context, the phenomenon of dysbiosis of gut microbiota (DOGMA) has begun to gain traction in PCOS research and is typically defined by a reduction in alpha diversity, an increase in LPS-producing bacteria, and a decrease in spore-forming species. Interestingly, gut dysbiosis is more severe in obese women with PCOS who have higher rates of insulin resistance. To address said insulin resistance in PCOS, myo-inositol is routinely employed and has been described as a safe and effective treatment for improving metabolic parameters, reducing hyperandrogenism and restoring ovulation. Myo-inositol has demonstrated a similar efficacy to the insulin-sensitizing drug metformin, albeit without the frequently observed gastrointestinal issues [7]. Despite the reported efficacy of myo-inositol supplementation, 30% of women are unresponsive to treatment, likely due to poor inositol bioavailability caused by impaired intestinal absorption. To counteract this, α-lactalbumin, a globular whey present in human milk, was identified owing to its prebiotic biological activities, which can restore intestinal flora improving the absorption of nutrients and reduce dysbiosis and inflammation. Most importantly, α-lactalbumin regulates the kinetics of intestinal tight junction opening, allowing for increased passive transport of inositol across the gut membrane. As a result of combination with α-lactalbumin, plasma myo-inositol is increased by 27.5% compared to myo-inositol alone [8]. In a recent study of PCOS patients who did not respond to myo-inositol, a subsequent follow-up treatment with myo-inositol and α-lactalbumin restored ovulation in 86% of cases [9]. This study demonstrated that the co-administration of myo-inositol and α-lactalbumin has a synergistic effect which is more efficacious than myo-inositol alone in PCOS patients [10]. Based on the reported findings, it is evident that moving forward myo-inositol should be co-administered with α-lactalbumin to maximize its potential in PCOS.

Targeting PCOS Phenotypes with a Tailored Treatment

The term PCOS puts undue focus on the "ovarian cysts" that are now known to be arrested follicles rather than cysts. Furthermore, the syndrome is more readily characterized by the presence of hyperandrogenism and metabolic factors, thus this may mislead physicians and patients alike, suggesting a name change may be required. Furthermore, patients are frequently considered a uniformed group, whereas stratification according to the presented clinical subtype would allow for a personalized, more effective therapeutic approach. To date, many patients are still classified using the Rotterdam criteria, which groups the three hyperandrogenic PCOS phenotypes (A, B, and C) along with the normoandrogenic phenotype (D). It is the opinion of the EGOI-PCOS that hyperandrogenic and normoandrogenic PCOS should be considered two separate conditions with distinct etiopathogenesis. This hypothesis is supported by the inherent connection between metabolic disturbances – such as insulin resistance – and hyperandrogenism, with hyperandrogenic patients (phenotypes A, B, and C) commonly presenting elevated BMIs and insulin resistance. In contrast, phenotype D patients typically present with a leaner profile and without insulin resistance, and the distinction between the 2 patient groups is of great importance when selecting PCOS therapies that seek to correct the metabolic imbalance. Consequently, the EGOI-PCOS group has chosen to reclassify phenotypes A, B, and C as an endocrine-metabolic syndrome while phenotype D would remain PCOS as it lacks the metabolic involvement of the other phenotypes and is most likely a consequence of ovarian factors [11]. One possible explanation for the pathogenesis of phenotype D is altered levels of the growth factor IGF-1. To support this theory, a recent in-vivo study demonstrated that, while IGF-1 encourages follicular growth at low concentrations, at 50 ng/mL, IGF-1 has an inhibitory effect on follicular growth and causes menstrual cycle alterations [12]. It is apparent that given the likely differences in root cause between the two subtypes of PCOS, new classification systems are required to properly guide the therapeutic approach.

Conclusion Statement

Inositol therapy in PCOS has continued to gain interest in recent years, largely due to its acceptable safety profile in comparison to pharmaceutical insulin sensitizers such as metformin. It is, however, clear that inositol therapy must be tailored, with key factors such as the ratio between myo-inositol and D-chiro inositol, inositol absorbance rates, and the role insulin resistance plays in PCOS being considered. The ISGE 2024 EGOI-PCOS meeting served as a fruitful forum for an engaging discussion around the topic of inositol, and it is hoped that this report may serve as a catalyst for further much-needed studies.

Conflict of Interest Statement

V.U. is an employee of Lo.Li. Pharma S.R.L., and all other authors have no conflicts of interest to declare.

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Author Contributions

L.P., Z.K., M.N., S.H.M., and V.U. all assisted in conceptualization and writing the draft and final manuscript.

Data Availability Statement

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