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Inositol supplementation in the management of Polycystic Ovary Syndrome

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder associated with a broad spectrum of symptoms. The exact etiopathogenesis remains unclear. As a result, the therapeutic approach primarily focuses on alleviating symptoms. Inositol is a substance that plays a role in hormonal signal transduction. This study aims to determine whether inositol supplementation might be beneficial in PCOS management, as the traditionally implemented medications do not always meet the therapeutic expectations. PCOS causes a range of symptoms, resulting in various consequences. Physicians diagnose PCOS relying on clinical criteria, which include impaired ovulation, hyperandrogenism, and polycystic ovaries. The majority of patients suffer from insulin resistance as well. Consequently, one of the predominantly prescribed medications is metformin, which acts as an insulin-sensitising agent. Another approach is oral contraceptives. However, those therapeutic options are not suitable to every clinical situation, leaving patients and doctors in constant search for novel medications. One of them is inositol, which is especially beneficial in managing insulin resistance and irregular menstruation. In this review, we analyse 37 articles published between 2014 and 2024. Polycystic Ovary Syndrome is a serious health issue affecting a significant number of women of reproductive age. A growing number of studies investigate novel ways of managing PCOS, especially those leaning towards more natural agents that are physiologically occurring in the human body. Inositol supplementation is a promising therapeutic approach. Nevertheless, further investigation into the subject is crucial to define its role in PCOS treatment.

Keywords: inositol, PCOS, Polycystic Ovary Syndrome

1. INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a common hormonal disorder, first described in 1935 by Irving F. Stein, Sr., and Michael L. Leventhal. It is estimated

to affect approximately 10-15% of women of reproductive age (Monastra et al., 2017). The prevalence of PCOS might vary slightly depending on implemented diagnostic criteria and the population studied, and is ranging between 6% to 20% (Sanchez-Garrido & Tena-Sempere, 2020).

Manifestation of PCOS typically includes impaired ovulation, elevated androgens level and insulin resistance (Pourghasem et al., 2019). Consequently, patients suffer from irregular, infrequent menstrual bleeding and infertility, as well as hyperandrogenism symptoms such as hirsutism and/or acne (Formuso et al., 2015). Moreover, PCOS might lead to obesity or excess weight, which further causes an increase in estrogen levels and poses numerous hormonal and metabolic challenges. This phenomenon contributes to serious consequences i.e. increased cardiovascular incidents risk (Cirillo et al., 2020; Deepti et al., 2017). Therefore, the introduction of efficient treatment is vital in order to prevent these life-threatening consequences.

As the exact etiopathogenesis remains unclear, PCOS treatment depends on its presentation, primarily focusing on lifestyle changes to increase insulin sensitivity (Jamilian et al., 2017; Prabhakar et al., 2021) and maintain a healthy body weight, which is crucial to ensure proper symptoms management (Prabhakar et al., 2021). Metformin and oral contraceptives are commonly prescribed as a part of the pharmacological treatment (Prabhakar et al., 2021; Nordio et al., 2019). Additionally, ovulation-inducing agents might be used in fertility treatment (Pourghasem et al., 2019; Prabhakar et al., 2021).

As widely prescribed medications do not lead to the complete disappearance of symptoms and pose the risk of numerous side effects, there has been a constant search for novel therapeutic agents. One of them is inositol, particularly myo-inositol (MI) and D-chiro-inositol (DCI), a supplement thought to be beneficial in PCOS management. In the human body, it serves as a compound of phosphatidylinositol and its phosphate derivates, therefore playing the role of a structural basis for secondary messengers (Nordio et al., 2019). Consequently, inositol is involved in processes such as insulin signal transduction, thyroid hormone synthesis and FSH release (Deepti et al., 2017; Nordio et al., 2019).

PCOS presents significant challenges in clinical management, particularly due to the lack of a universally accepted therapeutic approach. While traditional medications have shown varying levels of efficacy, inositol supplementation has emerged as a promising alternative. This study aims to determine whether inositol leads to a decrease in PCOS symptoms, especially in comparison to other medications, and represents a new natural approach in PCOS treatment.

2. METHODS

In this review, we analyse the materials collected in the "PubMed" database. During the search for scholarly articles, we entered the following keywords: inositol and PCOS (Polycystic Ovary Syndrome). Additionally, we included relevant peer-reviewed articles. Studies were selected based on their focus on the mechanism of action of inositol and/or pathological processes occurring in PCOS.
A total of 37 articles published between 2014 and 2024 met the inclusion criteria.

Inclusion criteria:

Clinical trial, randomized controlled trial focusing on the topic of inositol supplementation in patients suffering from PCOS, published in English.

Exclusion criteria:

Studies with weak methodology and publications written in languages other than English.

3. RESULTS AND DISCUSSION

Symptoms of PCOS

Polycystic ovary syndrome diagnosis depends on clinical manifestations. Physicians predominantly use diagnostic criteria established by ESHRE/ASRM in Rotterdam, which consist of the main characteristics of PCOS. The criteria include oligoovulation and/or anovulation, excess androgen activity and polycystic ovaries determined by the ultrasound (Nordio et al., 2019; Szczuko et al., 2021). In spite of being seemingly unrelated, all the mentioned symptoms are associated with the phenomenon of hormonal imbalance.

Numerous women suffering from PCOS are insulin resistant (Szczuko et al., 2021; Montanino Oliva et al., 2018; Andavar et al., 2024) and/or obese, which might be preceded by hyperinsulinemia (Montanino Oliva et al., 2018; Gupta et al., 2016) in lean patients (Monastra et al., 2017). Additionally, dyslipidemia and low-grade inflammation occur more frequently in PCOS patients, which leads to an increase in the risk of type 2 diabetes and cardiovascular disease (Cirillo et al., 2020; Deepti et al., 2017). This phenomenon also poses long-term health concerns throughout the lifespan (Monastra et al., 2017).

Moreover, elevated insulin levels influence the hypothalamic-pituitary-ovarian axis (Tagliaferri et al., 2017). As a result, hypothalamus releases GnRH in more frequent pulses, leading to increased LH/FSH ratio (Özay et al., 2019). Increased LH stimulates primordial follicles and promotes ovarian follicles development (Pacchiarotti et al., 2016). Nevertheless, as a result of disturbed ovarian function, the maturation of the follicules is decreased, which is observed in ultrasound as the presence of so-called cysts (Monastra et al., 2017). Subsequently, the lack of adequate follicle development and its improper selection causes infrequent ovulation. This phenomenon is clinically apparent because of irregular menstruation and infertility (Emekçi Özay et al., 2017).

Furthermore, increased frequency of GnRH pulses results in increased ovarian androgen production and diminished SHBG release (Monastra et al., 2017; Emekçi Özay et al., 2017). Simultaneously, elevated insulin contributes to increased 17-alpha-hydroxylase activity, which converts progesterone to androstenedione. As a consequence, patients with PCOS suffer from features caused by hyperandrogenemia, i.e., hirsutism and acne (Troisi et al., 2019).

Not only does excess body weight contribute to elevated insulin levels, but it also contributes to excessive adipose tissue (Couto Alves et al., 2017), which in turn produces aromatase. Subsequently, aromatase converts blood androgens to estrogens, which inhibit FSH release (Pourghasem et al., 2019) and further increase LH/FSH imbalance.

Treatment of PCOS

Because of the complex pathogenesis and the broad spectrum of clinical manifestations of PCOS, physicians adjust the therapeutic approach to the patient's phenotype. Regular physical activity and a balanced diet are generally beneficial for most people. So, they are for women suffering from PCOS, especially with concomitant insulin resistance or obesity (Hernandez Marin et al., 2021). Nevertheless, medications may be vital in supporting non-pharmacological treatment (Fruzzetti et al., 2017).

One of the most recommended medications in PCOS management is metformin, which increases insulin sensitivity (Jamilian et al., 2017). This action leads to the lowering of blood glucose and insulin levels, therefore alleviating the symptoms of insulin resistance (Özay et al., 2019) as well as decreasing ovarian androgen production, which leads to reduced circulating androgen levels (Monastra et al., 2017).

Another common approach is oral contraceptives (Formuso et al., 2015), mainly combined oral contraceptives (estro-progestin compounds). They are beneficial in irregular menstrual bleeding and hyperandrogenism, since estrogens and progestins suppress the release of LH. Subsequently, there is a decrease in ovarian androgen production. Nevertheless, not only do estrogens suppress the LH, but also lead to the increase of the synthesis of SHBG in the liver. This results in the lowering of circulating free androgen levels. Furthermore, estrogens promote the peripheral block of androgen receptors.

The triple mechanism of anti-androgenic action of oral contraceptives greatly improves the efficacy in hirsutism management. However, this approach is not suitable for women actively trying to conceive (Monastra et al., 2017). In PCOS patients who have infertility, ovulation-stimulating agents (eg. clomiphene, letrozole) improve the chances of conception (Pourghasem et al., 2015). Nevertheless, in some cases, IVF or even ICSI might be essential to conceive.

Natural approach

In recent years, there has been a surge in the search for novel ways of healing metabolic disturbances such as PCOS. One approach is the supplementation of inositol, a physiological compound of phosphatidylinositol. Its phosphate derivatives are essential in the production of second messengers, which regulate hormones such as GnRH (Abbara et al., 2020), TSH, and insulin (Nordio et al., 2019). Among nine existing inositol stereoisomers, the most commonly occurring in the human body are myo-inositol and D-chiro-inositol (Nordio et al., 2019; Mendoza et al., 2019), which are the focus of this study.

MI and DCI are mediators of different insulin actions. Both isomers take part in the synthesis of inositolphosphoglycan (IPG) insulin second messengers, which leads to their transformation to, accordingly, MI-IPG and DCI-IPG. Consequently, MI-IPG is involved in cellular glucose uptake in the ovary among other tissues. It is also crucial in FSH signaling. When it comes to DCI-IPG, it plays a significant role in glycogen synthesis and insulin-mediated androgen synthesis. Moreover, both MI and DCI lead to a lowering of testosterone and LH levels and, consequently, to a decrease in the LH/FSH ratio. Subsequently, the symptoms of hyperandrogenism are decreasing, which justifies the purpose of including either MI or DCI in the treatment (Nordio et al., 2019).

In comparison to healthy women, insulin-resistant PCOS patients experience a diminishment of the MI/DCI ratio. This phenomenon might be contributing to their symptoms, since the conversion of MI to DCI is under the control of insulin stimulus, determined by the individual cell metabolism. Thus, tissues with a significant storage of glycogen have greater DCI concentration than

tissues that consume the most considerable amounts of glucose. In states of reduced insulin sensitivity, the epimerization to DCI is lower. Nevertheless, this phenomenon does not apply to the ovary, which, on the contrary to the other tissues, hardly ever becomes resistant to insulin. As a result, hyperinsulinemia causes the overproduction of DCI (Unfer et al., 2014).

Inositol-based therapy is particularly promising due to its association with the mentioned pathomechanisms occurring in PCOS. Furthermore, inositol causes no side effects (Jamilian et al., 2017; Nordio et al., 2019; Montanino Oliva et al., 2018; Hernandez Marin et al., 2021; Morgante et al., 2015), and its supplementation is considered safe. However, long-term studies are crucial to exclude potentially fatal, far-reaching consequences and determine the safety of inositol administration. On the contrary, metformin might lead to frequent (mainly gastrointestinal) adverse effects (Jamilian et al., 2017; Nordio et al., 2019; Özay et al., 2019; Hernandez Marin et al., 2021), while oral contraceptives are not an adequate approach in patients trying to conceive (Nordio et al., 2019).

Inositol supplementation in PCOS

Inositol supplementation has been the subject of extensive studies for its potential to alleviate the symptoms of PCOS. The researchers obtained promising results in improving insulin resistance, regulating menstrual cycles, and reducing hyperandrogenism. This section reviews key findings from recent studies that compare the efficacy of inositol with other standard treatments, such as metformin and oral contraceptives.

In numerous studies inositol has been shown to reduce insulin resistance (Formuso et al., 2015; Cirillo et al., 2020; Deepti et al., 2017; Prabhakar et al., 2021; Nordio et al., 2019; Andavar et al., 2024; Tagliaferri et al., 2017; Özay et al., 2019; Hernandez Marin et al., 2021; Fruzzetti et al., 2017; Kachhawa et al., 2022; Shokrpour et al., 2019; Rajasekaran et al., 2022; Soldat-Stanković et al., 2022) or improve metabolic well-being in general (Jamilian et al., 2017; Hassan et al., 2023; Pkhaladze et al., 2021; Agrawal et al., 2019), with similar results to metformin (Formuso et al., 2015; Jamilian et al., 2017; Andavar et al., 2024; Tagliaferri et al., 2017; Fruzzetti et al., 2017; Rajasekaran et al., 2022; Soldat-Stanković et al., 2022). In two studies, MI was more effective in lowering insulin levels and fasting plasma glucose than metformin (Shokrpour et al., 2019; Hassan et al., 2023). One study (Prabhakar et al., 2021) obtained insignificant results, however in favour of MI.

According to one study, a combination of inositol and metformin has provided additional benefits compared to metformin alone in terms of menstrual frequency and quality of life (Nazirudeen et al., 2023). Another study has also highlighted the positive influence of this drug combination on menstrual bleeding frequency. In this study, an addition of inositol has also facilitated conception and increased the number of live births. However, no further improvement in biochemical and metabolic parameters has been proved (Pourghasem et al., 2019).

Regarding further metabolic disturbances, PCOS patients are exceptionally prone to dyslipidemia, which is a serious concern. In one study, MI improved features of metabolic syndrome, i.e., decreased triglycerides and LDL while increasing HDL cholesterol (Deepti et al., 2017). Andavar et al., (2024) compared effects of metformin to acarbose plus metformin to acarbose plus MI. The MI group obtained the most significant reduction in TGL and LDL levels. However, only the patients taking metformin and acarbose simultaneously gained a significant HDL increase. No influence on total cholesterol or VLDL was observed in any of the groups. On the other hand, according to Shokrpour et al., (2017), MI is more efficiently reducing triglycerides and VLDL levels than metformin. We believe the inconsistency in the obtained results might be associated with the additional administration of acarbose in one study and/or the small number of participants, as only one of the applicable trials recruited 168 participants and the other two even fewer.

Another study examined whether supplementation of MI and alpha-lactalbumin (alpha-LA) in MI-resistant patients leads to the lowering of triglycerides and total cholesterol levels (Montanino Oliva et al., 2018). Alpha-LA is a milk protein found in mammals, believed to increase inositol cell concentration (Hernandez Marin et al., 2021). Although the addition of alpha-LA significantly improved the lipid profile as well as MI plasma levels, the mechanism remains uncertain and requires further investigation.

Moreover, inositol is beneficial in the management of excess body weight since it leads to a decrease in BMI (Troisi et al., 2019; Hernandez Marin et al., 2021; Fruzzetti et al., 2017; Soldat-Stanković et al., 2022; Pkhaladze et al., 2021). One study has indicated weight reduction in lean teenagers (13-16 years old) with PCOS treated with MI, while only prevention of BMI increase occurred in 17-19-year-olds who supplemented MI and received oral contraceptives. Patients of bigger weight are more likely to benefit from inositol supplementation, as they obtain greater weight loss (Pkhaladze et al., 2021). However, in one study, inositol had no impact on body weight, on the contrary to metformin, which led to weight loss (Tagliaferri et al., 2017). One study has shown no changes in BMI in patients treated with acarbose and MI, as well as in patients treated with acarbose and metformin (Andavar et al., 2024).

Regarding hyperandrogenism and its clinical traits, the authors of the considered studies implemented several ways of its measurement. Hernandez Marin et al., (2021) and Morgante et al., (2015) reported a decrease in androstenedione levels as a result of MI administration. Five studies showed a decrease in testosterone levels (Jamilian et al., 2017; Nordio et al., 2019; Morgante et al., 2015; Hassan et al., 2023; Mendoza et al., 2020). Two of them indicated greater action of MI than metformin (Jamilian et al., 2017) or metformin with pioglitazone (Hassan et al., 2023).

Jamilian et al., (2017) and Hassan et al., (2023) measured hirsutism in Ferriman-Gallwey Score, which decreased more significantly in patients supplementing MI in comparison to those treated with metformin. In one study, owing to administration of MI with monacolin K and lipoic acid, Ferriman-Gallwey Score decreased (Morgante et al., 2015). On the other hand, one study indicated reduced efficacy of inositol (measured in Ferriman-Gallwey Score) in comparison to metformin (Tagliaferri et al., 2017).

In one study, the authors measured changes in acne using the Acne Score, concluding that acne decreases similarly in patients treated with metformin and those supplementing with MI (Formuso et al., 2015). Nevertheless, three studies have shown no influence of inositol either on androstenedione level (Cirillo et al., 2020), circulating free androgen levels (Tagliaferri et al., 2017) or hirsutism and acne (Fruzzetti et al., 2017). We believe the variety of applied methods of hyperandrogenism measurement and the broad spectrum of individual differences in PCOS presentation might be responsible for existing inconsistencies in the results.

Another problem faced by PCOS patients is infrequent menses, which inositol supplementation might well tackle. A combination of MI and DCI resumes menstruation in patients with amenorrhea (Kachhawa et al., 2022) and increases cycle frequency (Formuso et al., 2015; Nordio et al., 2019; Kachhawa et al., 2022). MI/DCI 40:1 ratio leads to the most significant results (Sanchez-Garrido & Tena-Sempere, 2020; Nordio et al., 2019; Mendoza et al., 2019).

Three studies also focused on comparing MI to metformin concerning cycle regulation efficacy. However, the results were quite diverse. About 50% of the participants of one study obtained normalisation of the menstrual cycle, regardless of the implemented treatment (Fruzzetti et al., 2017). Another study, however, denied the influence of inositol on menstrual bleeding frequency and indicated the efficacy of metformin (Tagliaferri et al., 2017). This inconsistency might be due to the difference in the prescribed dosage of metformin and MI. 1500 mg of metformin per day and 4 g of MI led to similar results, while 850 mg of metformin per day was more efficient than 2 g of MI in menses regulation. Additionally, in one study, MI with resveratrol has been more effective in regulating menstruation than a combination of metformin and pioglitazone (Hassan et al., 2023). Nevertheless, two studies have shown metformin and MI acting synergistically in order to improve cycle frequency (Nazirudeen et al., 2023; Agrawal et al., 2019).

Polycystic ovary syndrome might be extraordinarily distressing because of infertility. In this matter, inositol is exceptionally promising, as it seems to facilitate ovulation or ovulation induction (Emekçi Özay et al., 2017) and increase pregnancy chances (Emekçi Özay et al., 2017; Akbari Sene et al., 2019) as well as live birth rates (Agrawal et al., 2019). In pre-treatment in the GnRH-antagonist cycle, MI is more efficient than metformin in facilitating conception and equally efficient in Ovarian Hyperstimulation Syndrome (OHSS) prevention (Rajasekaran et al., 2022). In letrozole or clomiphene-induced ovulation, studies indicated greater MI action (Pourghasem et al., 2019; Rolland et al., 2017). However, the results were insignificant. One study also focused on MI and melatonin supplementation, showing its positive influence on oocyte and embryo quality (Pacchiarotti et al., 2016).

Two studies focused on determining the best ratio of inositol stereoisomers in infertility treatment in PCOS patients. Patients receiving 550 mg of MI and 150 mg of DCI before ICSI or IVF procedures were more likely to conceive and give birth to a live newborn than patients receiving 550 mg of MI and 13,8 mg of DCI. Furthermore, they were less likely to develop OHSS (Mendoza et al., 2019). Moreover, patients receiving 550 mg of MI and 300 mg of DCI for twelve weeks before ICSI were more likely to have oocytes of better quality than patients receiving 550 mg of MI and 27,6 mg of DCI (Mendoza et al., 2020). However, in another study, greater MI/DCI ratio in follicular fluids was associated with better follicular development of the oocyte collected in order to conduct IVF (Ravanos et al., 2017).

Due to the frequent occurrence of low-grade inflammation in PCOS (Deepti et al., 2017; Couto Alves et al., 2017), two studies investigated whether MI might lead to a reduction in inflammation. MI supplementation reduces CRP plasma levels in women with PCOS (Jamilian et al., 2017) and in women with PCOS and periodontitis (Deepti et al., 2017). Furthermore, MI downregulates the IL-1 gene. Unfortunately, it appears to have no effect on plasma nitric oxide or gene expression of IL-8 and tumor necrosis factor alpha (Jamilian et al., 2017).

4. CONCLUSIONS

Polycystic Ovary Syndrome is a common health issue responsible for numerous challenges associated with metabolic and hormonal imbalance, such as insulin resistance and obesity, hirsutism and acne, oligoovulation and infrequent menses, as well as infertility. The mentioned problems impact a patient's well-being on many levels, leading to a constant search for novel remedies.

Based on our research, inositol supplementation might contribute significantly to the alleviation of main PCOS symptoms and improve life quality. It is a valid alternative to commonly prescribed medications. Our research highlighted that insulin-resistant women unquestionably benefit from inositol administration. Furthermore, it is beneficial in managing excess body weight and dyslipidemia. Inositol also decreases hyperandrogenism. However, as the methods for measuring hyperandrogenism vary and are not directly comparable between studies, we believe that conducting further research is essential. Although some studies indicate a positive influence of inositol on fertility, the available data are sparse and require further investigation. Regarding the most beneficial therapeutic approach in specific clinical situations, continuous research is vital, as each PCOS case is unique and requires an individualized approach.

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Ethical approval

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Conflict of interest

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Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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