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The Impact of Inositol Supplementation on Menstrual Cycle Regularity and Quality of Life in Those with Polycystic Ovarian Syndrome: A Narrative Review

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Abstract

Approximately ten percent of patients of childbearing age are diagnosed with Polycystic Ovarian Syndrome (PCOS) in the United States, a condition that is a common cause of infertility. For some, a PCOS diagnosis may come before any plans to become pregnant. For this group of patients, addressing menstrual cycle regularity may lower anxiety related to breakthrough bleeding, add to emotional well-being, and improve overall quality of life. This review summarizes the quantitative research on inositol as a therapy for menstrual cycle regularity and quality of life in patients with PCOS. It also identifies implications for the therapeutic use of inositol to improve outcomes for patients with PCOS who are not actively pursuing pregnancy. As a result of the review, it can be concluded that inositol supplementation supports menstrual cycle regularity and improves quality of life in all patients diagnosed with PCOS. Additional research is needed regarding nutritional therapies for PCOS patients who wish to improve their reproductive system health outside of the context of fertility.

Keywords: PCOS: Polycystic Ovarian Syndrome; Inositol; Oligomenorrhea; Menstrual cycle regularity; PCOS QOL

Introduction

Polycystic Ovarian Syndrome (PCOS), initially named Stein-Leventhal syndrome, is a multifaceted condition that impacts patients of childbearing age [1]. In the United States of America, approximately 10% of women have been officially diagnosed with PCOS. However, it is generally accepted that many more patients have the condition and do not yet know [2].

While PCOS is named for its characteristic polycystic ovaries, many patients with PCOS have normal ovaries. It is now believed that altered insulin signaling, increased production of androgens during ovarian steroidogenesis and reduced sex hormone-binding globulin production are the primary causes of PCOS symptom manifestation. Additionally, obesity, previously thought to contribute to the syndrome's progression, has recently been proven less impactful, as lean women and obese women with PCOS show similar insulin resistance levels [3,4].

Risk factors for PCOS include being of childbearing age, being 12 years or younger at menses onset, having a family history of PCOS having a waist circumference over 35 inches obesity, having MTHFR polymorphisms, gastrointestinal dysbiosis and routinely consuming a diet with excessive refined carbohydrates [1,5-9]. PCOS is associated with several comorbidities, including obesity, infertility, miscarriage, hirsutism, type 2 diabetes mellitus, hypercholesterolemia, cardiovascular disease, insulin resistance, oligomenorrhea and amenorrhea (Torres et al., 2018). Ovulatory dysfunction associated with oligomenorrhea and amenorrhea is one of the diagnostic criteria for PCOS (Escobar-Morreale, 2018). The majority of research on PCOS treatment is centered around ovulation and fertility. However, these adverse effects reduce Quality Of Life (QOL) for all patients diagnosed with the condition, including those who have no plans to become pregnant [10].

PCOS and its impact on quality of life

QOL for PCOS patients has been measured with various surveys and questionnaires, the most popular being the short form health survey and the Polycystic Ovary Syndrome health-related Quality of life Questionnaire (PCOSQ). These surveys ask about patient perceptions regarding their PCOS symptoms, including hirsutism, infertility, vitality, mental health, and menstrual cycle regularity [10]. Perceived QOL is lower in women and adolescent girls with PCOS [11].

Menstrual cycle irregularity consistently polls among the symptoms that most negatively impact QOL in patients with PCOS. This may be because it is one of the most common symptoms of PCOS, especially among adolescents (De Sousa et al., 2016). Irregular periods can cause inconveniences to everyday life. It may often result in breakthrough bleeding, which may cause embarrassment for some. The oligomenorrheic and amenorrheic states caused by PCOS also put patients at higher risk for endometriosis (Escobar-Morreale, 2018). Anxiety and depression are common comorbidities in patients with PCOS [12].

In one study of the symptoms of 174 women diagnosed with PCOS, menstrual cycle irregularity was noted as a predictor of lower quality of life and depression (Alisghari et al., 2016). When polling patients with PCOS who were not actively seeking pregnancy, PCOSQ scores for the "menstrual problems domain" were among the lowest at 3.9/7 [13]. In a different study using the PCOSQ, menstrual cycle irregularity, including amenorrhea and oligomenorrhea, resulted in the lowest QOL score of all symptoms [14].

Inositol insulin signaling and glucose metabolism

Inositol (hexahydroxycyclohexane) is a cyclic prebiotic carbohydrate with six hydroxyl groups. It was discovered and named by Johanes Joseph Scherer in 1850 when he extracted it from glycogen stored in muscle. Inositol has nine stereoisomers. Two are proven insulin mediators; Myoinositol (MYO) & D-Chiro-Inositol (DCI). Inositol is converted from G6P, isomerized by D-3-myoinositol-phosphate synthase to Inositol-3-Phosphate (Ins3P), and dephosphorylated by Inositol Monophosphatase-1 (IMPA-1). The result of this process is the inositol stereoisomer, MYO [15].

There are two groups of MYO transport systems; sodium ion-coupled transporters found in all animals and proton-coupled transporters found in all eukaryotes [15]. SMIT1 and SMIT2 sodium ion-coupled transporters are the two transporters involved in inositol transport. They are controlled by the phosphorylation of protein kinase A and C and the HMIT1 transporter. Because SGLT1 and SGLT2 prevent both glucose and inositol uptake in hepatocytes, and because MYO inhibits glucose absorption and glucose depletes MYO, it is believed that glucose and MYO both vie for the same transporter [16]. As insulin is produced, hepatocytes release Inositol Phosphoglycans (IPGs) containing MYO, or DCI. MYO may be converted to DCI by NAD/NADH epimerize [4]. Consequently, low MYO concentrations lead to low DCI concentrations [16]. There are higher concentrations of DCI in muscle and the liver (glycogen storage tissues) and higher concentrations of MYO in the brain and ovaries (high-energy glucose utilization tissues) [3]. Inositol homeostasis is maintained through intestinal absorption, waste excretion, synthesis, and catabolism [15].

MYO and DCI mimic insulin and act as second messengers of insulin receptors. When insulin receptors are activated, MYO and DCI are released from the cell and reimported by a transporter [8]. While MYO & DCI are both insulin sensitizers, MYO is most closely linked to cellular glucose uptake, while DCI is most closely associated with glycogen synthesis [33]. MYO & DCI reduce hyperglycemia by promoting muscular glycogenesis and triggering glucose metabolism in the Kreb's cycle [16].

Humans can synthesize up to 4 grams of inositol per day from glucose [16]. Because the human body can synthesize inositol, there is no dietary baseline for inositol consumption. Synthesis occurs mainly in the kidney, but the brain, testes, and ovaries can also produce inositol [15]. In addition to inositol synthesis, the typical American diet provides about 500 mg-600 mg of inositol daily [17]. Those who consume diets with daily intakes of whole grains, legumes, nuts, and seeds, intake even higher amounts since they are rich sources of phytic acid and phytates.

Phytic acid and phytates contain inositol in the forms of phosphatidylinositol and inositol P6. Since inositol is found in fibrous foods, diets high in fiber help prevent and manage PCOS, whereas diets low in dietary fiber and high in refined grains contribute to the condition [16]. People, who have a history of long-term antibiotic use, consume large amounts of caffeine, eat a diet high in refined and processed foods, and do not eat vegetables daily may need to supplement with inositol to keep levels regular [15].

Insulin resistance significantly impacts inositol synthesis, transport, and absorption. It modifies the MYO to DCI ratio in tissues, blood, and urine, worsens insulin resistance, impairs redox reactions, and increases oxidative stress [16]. Hyperglycemia reduces MYO uptake and incorporation into phospholipid bilayer. It also supports MYO depletion in sodium ion-coupled transporters, but proton-coupled transporters are not impacted by glucose concentration [15]. Because of these consequences, an imbalanced ratio of MYO to DCI is a marker of insulin resistance [4].

Inositol's impact on menstrual cycle regularity in patients with PCOS

30%-80% of patients with PCOS are insulin resistant [3]. As a result, prescription drugs like insulin sensitizers, aromatase inhibitors, or oral contraceptives are commonly used as treatment but often induce unwanted side effects that can negatively impact a patient's quality of life (Escobar-Morreale, 2018). Therefore, many clinicians have sought more to learn about and use more natural therapies like inositol to include in their protocols for PCOS treatment. In recent years, MYO and DCI have become common treatments for PCOS [4]. Inositol has been shown to decrease hyperandrogenism and insulin resistance, restore ovarian function, increase fertility, and improve menstrual cycle regularity in patients with PCOS [4]. Many variations in dosages of the isomers have been proven effective (see Table 1).

Study design	Participant demographics	Treatment & dosage	Results related to menstrual cycle
RCT [17]	50 women with PCOS per Rotterdam criteria	500 mg metformin 3 times daily versus 4 g MYO + 400 mcg folic acid daily for six months	Menstrual cycle length in days decreased from 119 to 54 in the Metformin group ($p<0.001$).

			Changes in menstrual length occurred in 80% of the metformin group and 82% of the MYO group. No differences in menstrual cycle regularity between groups
RCT [18]	120 women with PCOS - 20-38 years old - BMI < 30 kg/m^2	500 mg metformin + 600 mg MYO 3 times daily versus 500 mg metformin 3 times daily for 3 months	Days of bleeding decreased from 4.83 to 4.57 in MYO + metformin group versus 4.4 to 4.34 in the Metformin group (p=0.01) [Greater improvement in the MYO+metformin group] Menstrual cycle length in months decreased from 2.15 to 1.25 in MYO + metformin group versus 2.04 to 1.13 in metformin group (p=.03) [Statistically significant changes in both groups, but not between groups]
RCT [19]	43 patients with PCOS	Group 1: Diet for 6 months Group 2: Diet+4 g MYO+400 mcg folic acid for 6 months Group 3: Diet+1.1 g MYO+27.6 mg DCI+400 mcg folic acid for 6 months	All groups: Menstrual regularity increased Group 3 had the highest rate of menstrual regularity restoration (p=0.02)
RCT [20]	45 overweight patients with PCOS	Group A: 2 g MYO+200 mg folic acid daily for 12 weeks Group B: 200 mg folic acid daily for 12 weeks	Menstrual cycles in all Oligomenorrhea and amenorrhea Group A participants were restored. No changes in menstrual cycle occurred in Group B.
Retrospective Study [21]	44 women with PCOS and oligomenorrhea	800 mg MYO+2000 mg alpha lipoic acid daily for 24 months (mean treatment duration was 13 months)	Menstrual cycle was reduced from a mean of 69 days to 43 days at 6 months, to 38 days at 12 months to 35 days after 24 months of treatment. Menstrual cycle was normalized in all participants
RCT (Le-Donne et al, 2012)	27 overweight/obese patients with PCOS	Group 1: Diet Group 2: Diet+1000 mg Metformin daily Group 3: Diet+500 mg Metformin+4 g MYO+400 mcg folic acid daily for three months	Menstrual cycle regularity was significantly restored in Group 3 (p<0.05), but not in Groups 1 or 2
Prospective Cohort Study (Lagana et al, 2014)	48 female patients with PCOS and oligo and amenorrhea	1 g DCI+400 mcg folic acid daily for six months	30 cases (62.5%) experienced improvements in menstrual cycle regulation by at most the 4th month of treatment (p<0.05)

Prospective Cohort Study [22]	37 subjects with an ovulatory PCOS	2 g MYO twice daily for three months, then 2 g MYO+50 mg alpha lipoic acid for 3 months	62% of women ovulated with MYO, and 86% ovulated with MYO+ALA
Clinical Trial [23]	56 patients with PCOS	2 g of inositol in the following MYO:DCI ratios: DCI alone 1:3.5 2.5:1 5:1 20:1 40:1 80:1	DCI alone-0/8 patients menstruated 1:3.5-0/8 patients menstruated 2.5:1-0/7 patients menstruated 5:1-1/8 patients menstruated 20:1-3/8 patients menstruated 40:1-5/8 patients menstruated 80:1-4/8 patients menstruated 40:1 was the most effective ratio to restore menses
RCT [24]	50 overweight women with PCOS	Group 1: 2 g MYO powder Group 2: 550 mg MYO+13.8 mg DCI	Both groups experienced similar rates of increased ovulation
Crossover Randomized Controlled Study [25]	27 overweight or obese oligoamenorrheic women with PCOS	850 mg Metformin twice daily for 6 months, then 2 g MYO twice daily for 6 months	Metformin improved menstrual regularity, MYO showed no change in improvement, but no decline is noted

Table 1: Inositol treatment and results in patients with PCOS.

MYO counters PCOS-associated metabolic syndrome and improves ovulation frequency [9]. In women with PCOS, it has been postulated that DCI mainly reduces hyperinsulinemia and MYO mainly improves menstrual cycle regulation [24]. The ratio of MYO to DCI is 100:1 in women without PCOS and 0.2:1 in women with insulin resistance and PCOS [33]. MYO levels are significantly lower in the follicular fluid of those with PCOS, & DCI is significantly higher than in women without PCOS [33].

The Permanent International and European School in Perinatal Neonatal and Reproductive Medicine organized the 2013 International Consensus Conference on Myo-inositol and d-chiro-inositol in Obstetrics and Gynecology, including opinion leaders in cell biology, endocrinology, and obstetrics and gynecology suggest that PCOS treatment be provided at a 40:1 MYO-to-DCI ratio to mimic standard ovarian ratios. They suggest that results are most likely seen at a dose of 2 grams inositol twice daily [13,26-35].

Conclusion

Inositol supplementation supports menstrual cycle regularity and improves quality of life in patients diagnosed with PCOS. While both MYO and DCI treatments improve PCOS-related oligomenorrhea and amenorrhea, more significant results are present when the two stereoisomers are combined. The most effective inositol dosage is between 2 and 4 grams daily, using a 40:1 MYO/DCI ratio. Additional research is needed regarding nutritional therapies for PCOS patients who wish to improve their reproductive health and quality of life outside of the context of fertility. Future research should focus more directly on this population and include global health assessments to assess quality of life as an independent outcome. Additionally, there is a deficit in the research directly connecting inositol to the improvement of QOL in patients diagnosed with PCOS.

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Conflict of Interest

The author declares no conflicts of interest.

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