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Polycystic ovary syndrome (PCOS) is a heterogeneous complex endocrine disorder characterized by oligo-ovulation, insulin resistance, and hyperandrogenism. Treatment should be individualized based on each patient's symptoms and reproductive goals. Unfortunately, there is no pharmacologic medication that simultaneously promotes ovulation, improves metabolic health, and reduces clinical hyperandrogenism. Metformin is a well accepted, evidence-based pharmacologic therapy that targets the insulin resistance pathway and improves ovulatory frequency, but it has limited effects on clinical hyperandrogenism as well as poor tolerability for some patients. The growing interest in complementary therapies has highlighted the need for more tolerable and 'non-pharmacologic' treatment options. Inositol, a naturally occurring compound, has gained attention as a promising therapeutic agent for managing PCOS. This review aims to support shared decision-making between clinicians and patients by exploring the roll of inositol as a complementary therapy for PCOS management.

Addressing Inositol Use in PCOS Management

Alyse Goldberg, MD

Introduction

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder characterized by hyperandrogenism, reproductive dysfunction, and insulin resistance. It is diagnosed by meeting 2 of the 3 Rotterdam criteria (hyperandrogenism, oligomenorrhea, and polycystic ovarian morphology).[1] However, as PCOS is a heterogenous condition that presents with a variety of symptoms of concern, therapy requires individualization. Current non-pharmacologic and pharmacologic therapeutic regimens aim to prevent complications such as endometrial hyperplasia and metabolic syndrome, while also managing symptoms of hyperandrogenism and oligo-ovulation/oligomenorrhea. These regimens may include targeting the insulin resistance pathway with lifestyle optimization and medications such as metformin to increase ovulation frequency or establishing endometrial protection with progesterone-containing

medications or combined estrogen and progesterone contraceptives. Anti-androgens may be used as an adjuvant therapy to combined oral contraceptive pills to target clinical symptoms of hirsutism or acne. Unfortunately, there is currently no pharmacologic medication that simultaneously promotes natural ovulation, improves metabolic health, and reduces clinical hyperandrogenism. Metformin is considered the gold standard pharmacologic therapy for targeting the insulin resistance pathway and has been shown to improve ovulatory frequency even in those without biochemical evidence of insulin resistance. However, it is not a perfect solution. Metformin is not efficacious in improving clinical hyperandrogenism,[1] and importantly, is associated with gastrointestinal side effects that limit achieving a therapeutic dose.

In this reproductive age population, many individuals may feel inadequately treated by available evidence-based therapies and may be targeted online with marketing for potential alternative therapies. Consequently, there is a growing interest in complementary therapies to improve health outcomes in PCOS.[2] Inositol, particularly in its forms of myoinositol isomer (MI) and D-chiro-inositol (DCI), has emerged as a promising therapeutic agent for managing PCOS symptoms. While there is a concern that this population may be vulnerable to marketing of costly, non-evidence-based therapies, empowering our patients to explore additional symptom management strategies can inspire greater motivation to adopt beneficial lifestyle changes, such as improved nutrition and regular activity, which are essential for living with PCOS. Thus, increasing our knowledge regarding popular supplements that may be "trending" may enhance our therapeutic relationships with our patients.

Inositol

Inositol, a sugar alcohol found naturally in plants and animals, was previously labelled as Vitamin B-8.[2] However, it is now known to be naturally present in foods such as fruits, beans, grains, and nuts. It has been touted as a supplement for PCOS and is available at health food stores and online in various forms, such as a white powder to dissolve in water, or in gel capsules. It is sold as either MI alone, DCI alone, MI+DCI combination, or with a variety of additives such as folic acid.

Myoinositol is the most abundant stereo-isomer of inositol in the human body. It plays various biological roles as a second messenger, including promoting glucose uptake in insulin transduction pathways, as well as in follicle-stimulating hormone (FSH)-mediated pathways affecting proliferation and maturation of granulosa cells in the ovary. Insulin stimulates the conversion of MI to DCI, which controls glycogen synthesis and insulin-induced androgen synthesis as well as cellular glucose uptake.

Hyperinsulinemia in the setting of PCOS may increase ovarian "epimerase" activity, leading to increased DCI synthesis. This adjustment alters the ratio of MI to DCI, favouring a higher DCI level and a lower than optimal MI level. This change is thought to contribute to the pathophysiology of PCOS by impairing insulin signalling and exacerbating hyperandrogenism.[3]

Inositol supplementation for PCOS has been suggested to improve insulin signalling pathways, leading to improved glucose metabolism, lower insulin levels, and potentially modest reductions in body mass index (BMI).[4] Its roll in FSH signalling may contribute to improved menstrual cycle regulation and ovarian function (thus reducing ovarian testosterone). By reducing insulin, inositol may improve sex hormone-binding globulin (SHBG) levels and support the physiological MI:DCI ratio, thereby facilitating the conversion of androgens to estrogen.

Guidelines

As part of the 2023 evidence-based PCOS guidelines,[1] the evaluation of inositol as a therapeutic option for PCOS was reviewed in section 4.7. The systematic review included 29 randomized controlled trials (RCTs) and 19 of these were included in the meta-analysis to determine recommendations. Ten studies had high risk of bias, 16 had a low or moderate risk, and 3 had an unclear risk of bias. The interventions and comparators were heterogeneous, which has led to concerns related to misinformation, and potential conflict of interest in the studies that support use of inositol. Since these supplements come at high financial cost, we need to ensure that evidence-based information is guiding their use.

As part of the recommendations in the guidelines, women taking inositol are encouraged to "advise their health professional[1]" if they are using complementary therapies. However, clinicians who refer to the guidelines will note the recommendation that "Specific types, doses or combinations of inositol cannot currently be recommended for adults and adolescents

with PCOS, due to a lack of quality evidence" (section 4.7.[4]).[1] Thus, how can we, as clinicians, adopt an evidence-based approach when the evidence does not meet the standards of clinical practice guidelines? Further, as a supplement rather than a medication, there are fewer clear regulations for commercially available products and less oversight regarding consistency within or between products and doses.

Therefore, the goal of this review is to complement these recommendations and inform shared decision-making with our patients who seek complementary therapy with inositol. As a medical community, we want to arm a vulnerable population with unbiased information to assist in navigating marketing campaigns of potentially expensive therapies with unclear benefits.

Described Effects of Inositol in PCOS

Metabolic Outcomes

Unfer et al. (2017) conducted a meta-analysis of 9 RCTs involving 496 participants with PCOS. Among the participants, 249 were in the control group and 247 received MI alone or combined with DI. The doses used were MI ranging from 1.1-4 g and/or DI ranging from 27.6-2400 mg/day over a period of 2 to 24 weeks. Their findings demonstrated that MI supplementation significantly decreased homeostatic model assessment for insulin resistance (HOMA-IR) and fasting insulin levels. This effect was most apparent after 24 weeks of administration, suggesting that improvements in metabolic outcomes may be time dependent. More recently, Greff et al.[5] found a significant reduction in BMI[5] (mean difference 0.45 kg/m^2), glucose levels (MD = -3.14; CI: -5.75, -0.54), and insulin values (MD = -2081.05, CI: -2745.32, -1416.78) compared with placebo in their meta-analysis. However, the authors acknowledged the presence of moderate and high risk of bias in some of these domains.

Hyperandrogenism

Inositol appears to play a role in the regulation of androgens. However, its effects on serum testosterone, androstenedione, and SHBG are inconsistent, depending on the dose of MI versus DI used. These results have been inconsistent across different meta analyses.[3,5] Despite these variances, as summarized in the 2023 guidelines, even if there may be biochemical improvement in androgens, no difference in hirsutism has been observed.[1]

Reproductive Outcomes

Pundir et al. conducted a meta-analysis that included 10 RCTs with 600 women with PCOS. The participants were treated with MI (doses ranging from 1.2-4 g), DI (doses ranging from 600-1200 mg), or placebo or metformin for 2 to 24 weeks. The study found that inositol improved ovulation rates and increased menstrual cycle frequency, but evidence for pregnancy, miscarriage, and live birth rates is lacking.

Additional proposed benefits of inositol are related to its role in advanced reproductive therapy. MI plays a potential role in FSH sensitivity and has been associated with reduced recombinant FSH dosing and fewer stimulation days needed during ovarian stimulation for in vitro fertilization (IVF).[6] Further, MI supplementation may improve the quality of oocytes and embryos in women undergoing IVF and intracytoplasmic sperm injection (ICSI) procedures, reducing the risk of hyperstimulation and potentially increasing the rates of successful pregnancies.[7]

Regarding its utility during pregnancy, a Cochrane review evaluated the potential of MI use to reduce gestational diabetes mellitus (GDM).[8] The authors concluded antenatal dietary supplementation with MI during pregnancy may reduce the incidence of GDM, hypertensive disorders of pregnancy, and preterm birth. However, they provided the caveat that current evidence is based on small studies that were not powered to detect differences in outcomes such as perinatal mortality, serious infant morbidity, and long-term implications.

Comparison to Metformin

Metformin has been considered the gold standard insulin sensitizer for managing PCOS. It has evidence to improve oligo-ovulation, prevent the progression of dysglycemia, and improve anthropometric measurements.[1] However, it may induce gastrointestinal side effects that prevent patients from reaching the therapeutic dose. The current literature comparing MI to metformin has a risk of bias[1] and still yielded results that were considered 'low certainty evidence' for all outcomes. Nonetheless, the meta-analysis conducted by Greff et al.,[5] found that inositol

showed non-inferiority compared to metformin in terms of improving cycle regularity.

Metformin has been rigorously studied and is currently recommended over inositol for improving central adiposity and cycle regularity if it is well tolerated.[1] However, inositol may serve as a "weaker" version of metformin for those who cannot tolerate it. It should be noted that some individuals report mild side effects from MI including nausea, dizziness, headaches, and gastrointestinal discomfort.[9]

Limitations

Dosing

Further research is necessary to establish optimal dosing regimens and long-term safety profiles for inositol. Over the past 10+ years, varying dosing regimens of MI powder have been studied and summarized.[6] The authors concluded that a dose of 4 g of MI with DCI at a ratio of 40:1 (MI:DI) is supported by many preclinical and clinical studies for targeting ovulation. They also highlighted that this consistency is not found in all supplements on the market. Further, the addition of other macro or microelements lack scientific rationale. However, an alternative "expert opinion" publication proposed that there may be a rationale for alternative ratios targeting fertility and pregnancy outcomes.[10]

It should be noted that when taken in gel capsule form, there may be improved gastrointestinal absorption, allowing for a reduction in dose by one-third compared to the powder form, with one published study suggesting an equivalent dose of 0.6 g MI in capsule form to 2 g MI in powder form.[11]

Varied Efficacy

As with most therapies, not all individuals will experience improvements in the targeted outcomes. One consideration is that specific phenotypes of PCOS may benefit more from inositol than others. However, it has been suggested that rather than focusing on phenotypes that would benefit, those with higher BMI or more significant insulin resistance may not experience as much benefit from inositol therapy as those without these co-morbidities.[12] No specific cut offs for these or any other co-morbidities have been provided to guide who would or would not be a good candidate for inositol therapy.

Summary

Inositol supplementation remains an accessible and potentially beneficial complementary therapy for patients. Ongoing research will be essential to fully elucidate its mechanisms of action, optimize treatment protocols, and identify those who would benefit most from these supplements. Regulation of products is needed to confidently integrate inositol into standard care practices for PCOS. As clinicians, we should consider therapeutic goals when counselling those interested in using inositol. Evidence supports targeting ovulatory frequency. However, the metabolic benefits are less clear. There have been observations of reduced fasting insulin and slight reductions in BMI without clear clinical implications. Importantly, there is limited observed changes to clinical hyperandrogenism.

Another concern is that there are no standardized dosing regimens. However, using 2 g of MI:DI powder at a 40:1 ratio twice daily appears to be the most acceptable approach. Lastly, the ideal duration of use and the implications of long-term use have not been determined.

Tips for counselling patients interested in trying inositol

- Emphasize lifestyle optimization and healthy behaviours as part of holistic care for PCOS.
- Have a therapeutic target in mind when starting therapies (e.g., menstrual frequency) and counsel patients that if insufficient, alternative pharmaceuticals are available (e.g., endometrial protection with progesterone or a combined oral contraceptive).
- Although some small studies have demonstrated a reduction in insulin parameters or androgens, these findings may not translate to clinically noted benefits.
- Anticipate that inositol is costly and unlikely to be covered by private or public insurance providers.
- Acknowledge that there may be inconsistencies between brands and within brands, as Health Canada does not regulate most inositol supplements.
- The dosing regimens and duration of therapy have not been established, and the long-term safety has not been adequately studied, raising concerns about potential unknown risks associated with prolonged use.

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References

1. Teede HJ, Tay CT, Laven JJE, Dokras A, Moran LJ, Pitonen TT, et al. Recommendations from the 2023 international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Eur J Endocrinol. 2023;189(2):G43-G64. doi:10.1093/ejendo/lvad096
2. Alesi S, Ee C, Moran LJ, Rao V, Mousa A. Nutritional supplements and complementary therapies in polycystic ovary syndrome. Adv Nutr Bethesda Md. 2022;13(4):1243-1266. doi:10.1093/advances/nmab141
3. Unfer V, Nestler JE, Kamenov ZA, Prapas N, Facchinetti F. Effects of inositol(s) in women with PCOS: a systematic review of randomized controlled trials. Int J Endocrinol. 2016;2016:1-12. doi:10.1155/2016/1849162
4. Dason ES, Koshkina O, Chan C, Sobel M. Diagnosis and management of polycystic ovarian syndrome [published correction appears in CMAJ. 2024 Mar 3;196(8):E269. doi: 10.1503/cmaj.240216.] [published correction appears in CMAJ. 2024 Mar 17;196(10):E351. doi: 10.1503/cmaj.240303.]. CMAJ. 2024;196(3):E85-E94. Published 2024 Jan 28. doi:10.1503/cmaj.231251
5. Greff D, Juhász AE, Váncsa S, Varadi A, Sipos Z, Szinte J, et al. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Reprod Biol Endocrinol. 2023;21(1):10. doi:10.1186/s12958-023-01055-z
6. Roseff S, Montenegro M. Inositol treatment for PCOS should be science-based and not arbitrary. Int J Endocrinol. 2020;2020:1-8. doi:10.1155/2020/6461254
7. Etrusco A, Laganà AS, Chiantera V, Buzzaccarini G, Unfer V. Myo-inositol in assisted reproductive technology from bench to bedside. Trends Endocrinol Metab. 2024;35(1):74-83. doi:10.1016/j.tem.2023.09.005
8. Motuhifonua SK, Lin L, Alsweiler J, Crawford TJ, Crowther CA. Antenatal dietary supplementation with myo-inositol for preventing gestational diabetes. Cochrane Database Syst Rev. 2023;2023(2):CD011507. doi:10.1002/14651858.CD011507.pub3
9. Dhaliwal J. Comparing metformin, inositol, and lifestyle modifications to improve symptomatology of polycystic ovary syndrome (PCOS): a research protocol. Undergrad Res Nat Clin Sci Technol URNCST J. 2022;6(11):1-8. doi:10.26685/urncst.409
10. Facchinetti F, Appetecchia M, Aragona C, Bevilacqua A, Bezerra Espinola MS, Bizzarri M, et al. Experts' opinion on inositols in treating polycystic ovary syndrome and non-insulin dependent diabetes mellitus: a further help for human reproduction and beyond. Expert Opin Drug Metab Toxicol. 2020;16(3):255-274. doi:10.1080/17425255.2020.1737675
11. Carlomagno G, De Grazia S, Unfer V, Manna F. Myo-inositol in a new pharmaceutical form: a step forward to a broader clinical use. Expert Opin Drug Deliv. 2012;9(3):267-271. doi:10.1517/17425247.2012.662953
12. Kamenov Z, Gateva A, Dinicola S, Unfer V. Comparing the efficacy of myo-inositol plus α-lactalbumin vs. myo-inositol alone on reproductive and metabolic disturbances of polycystic ovary syndrome. Metabolites. 2023;13(6):717. doi:10.3390/metabo13060717