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Investigating the Insulin Sensitizing Effects of Metformin and Myo-Inositol in Polycystic Ovary Syndrome: A Randomized Controlled Trial Protocol

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Introduction: Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by ovulatory dysfunction, hyperandrogenism, and metabolic dysregulation. Insulin resistance (IR) is a common hallmark of PCOS and contributes to metabolic dysfunction. A combination of lifestyle changes and symptom management treatments can help manage the condition. Metformin and myo-inositol (MI) have been shown to improve insulin sensitivity and reduce excess androgen levels in women with PCOS, but there is a lack of research on the effects of combinatory therapy of MI and metformin. This study aims to investigate the hypothesis that a combination of MI and metformin will result in improved insulin sensitivity and clinical outcomes of PCOS.
Methods: The study is a double-blinded, randomized controlled trial examining 60 women diagnosed with PCOS that demonstrate the presence of IR. Participants are randomized to one of the following treatments over a six-month period: metformin (MET), inositol (INO), combined metformin and inositol (MET-INO) or placebo-control (CON). BMI, LH:FSH ratio, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) were assessed at day 0, day 84 and day 168.
Anticipated Results: It is anticipated that the MET-INO group will have the most profound effects following intervention, with a decrease in BMI by 3-4%, a decrease in LH:FSH ratio by 30-40%, and a decrease in HOMA-IR by 1-1.5. MET group is expected to have a significant decrease in BMI by 2-3%, a decrease in LH:FSH ratio by 20-30%, and a decrease in HOMA-IR by 0.5-1.5. The INO group is anticipated to experience a significant decrease in BMI by 1-2%, a decrease in LH:FSH ratio by 10-20%, and a decrease in HOMA-IR by 0.2-0.4.
Conclusion: The findings of this study suggest that a combination therapy of metformin and MI may offer a more effective treatment option for improving insulin sensitivity in women with PCOS, compared to metformin or inositol treatment alone. These results have important implications for patients with PCOS and clinicians managing their care. Future studies should further investigate the effectiveness and long-term effects of these treatments.

Keywords: PCOS; insulin resistance; metformin; inositol

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women of reproductive age, that affects an estimated 1.4 million Canadians [1]. The etiology of PCOS is unknown, but it is believed to be related to a combination of genetic and environmental factors [2]. Methods of classification include the Adams criteria [3], the Rotterdam Consensus [4] and the Androgen Excess Society criteria [5]. These tools are used to assess for ovulatory dysfunction (anovulation, oligo-ovulation, and less than nine menstrual periods in one year), hyperandrogenism and/or polycystic ovarian morphology. PCOS is also associated with IR, acne, obesity, metabolic syndrome and menstrual irregularities [6-8].

A common hallmark for PCOS is insulin resistance (IR), that causes dysregulation of insulin to facilitate glucose uptake. Subsequently, this contributes to metabolic problems including weight gain, increased body mass index (BMI), metabolic syndrome, and type II diabetes mellitus [9]. Additionally, women with PCOS can experience a disruption in the ratio of luteinizing hormone to follicle stimulating hormone (LH:FSH). This is caused by a disturbance in the secretion pattern of the gonadotrophin-releasing hormone (GnRH). In women with PCOS, the elevated LH level can result in an overproduction of androgens, which disrupts normal hormone balance and can cause ovulatory dysfunction [10,11].

PCOS is a complex condition with no regulated treatments but is managed with a combination of lifestyle changes and symptom management treatments. Enhancing insulin sensitivity is a shared objective of these medical treatments. Metformin is a widely used medication that improves insulin sensitivity by enhancing peripheral glucose uptake and utilization while reducing hepatic glucose synthesis and intestinal glucose absorption [12]. Increased insulin sensitivity can then aid in the regulation of menstrual

cycles and ovulation, and the reduction of excess androgen levels and BMI [13]. Another known treatment is a naturally occurring carbohydrate called inositol. Myo-Inositol (MI) and D-Chiro-Inositol (DCI) are inositol isomers that have been investigated to improve insulin sensitivity, enhance ovarian function, and decrease excess androgen levels in PCOS [14,15]. It is important to note that while inositol has been shown to have potential benefits for people with PCOS, more research is needed to fully understand its effects and to determine the best form, MI or DCI, and dosages.

Although studies have compared the effects of inositol and metformin on IR in women with PCOS, there is a lack of research on the effect of combinatory therapy. It has been found that both inositol and metformin significantly improve insulin sensitivity in women with PCOS [16,17]. It is hypothesized that a combination of these two therapies will result in improved insulin sensitivity and a decrease in the LH:FSH ratio in patients with PCOS compared to each therapy alone. Furthermore, this study provides insights on clinical management of PCOS to improve quality care and health outcomes of women with PCOS.

Methods

Participants

The study is a double-blinded, randomized controlled trial that examines 60 insulin resistant women (30 ± 10 years, BMI of ≥ 25 kg/m²) diagnosed with PCOS according to the Rotterdam criteria. The following exclusion criteria are applied to the selection of participants: history of other endocrine disorders, including Cushing's syndrome, congenital adrenal hyperplasia, and thyroid dysfunction; history of diabetes, liver or kidney disease, or cardiovascular disease; patients currently taking medications that affect glucose metabolism or hormonal balance, including oral contraceptives and glucocorticoids; patients who are pregnant or breastfeeding; history of alcohol or drug abuse; and history of bariatric surgery.

Protocol

Participants are randomized to one of the following treatments: metformin (MET), inositol (INO), combined metformin and inositol (MET-INO) or placebo-control (CON). The study is conducted over a six-month period, during which the participants are screened for baseline measurements on day 0, followed by assessments at day 84 and day 168. The assessments include BMI (kg/m²), LH:FSH ratio, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). BMI of participants is measured by taking the precise weight and height measurements at assessment timepoints, the LH:FSH ratio is assessed by analyzing blood samples obtained from the participants. HOMA-IR is assessed by analyzing blood samples that measure the participants' fasting insulin and blood glucose. In addition, adherence to treatment is completed by participants using the Medication Adherence Rating Scale (MARS) at assessments stages.

Oral Administration

Participants randomized to intervention groups are instructed to take their respective tablets once daily with their evening meal for the duration of six-months. Participants randomized to receive MET are instructed to take two 500 mg tablets of metformin from the brand Glucophage. Participants randomized to INO are instructed to take two 2000 mg tablets of MI from the brand Organika. Participants randomized to MET-INO are instructed to take one 1000 mg tablet of metformin from the brand Glucophage and one 4000 mg of MI from the brand Organika. Participants randomized to CON are instructed to take two placebo starch tablets (Figure 1).

As part of the study protocol, all participants are instructed not to make any significant changes to their lifestyle such as physical activity, exercise programs or diets during the six-month study period. They are instructed not to begin any new medications or supplements, except for those provided by the study unless directed by health practitioner. During the initial screening, participants are informed of potential side effects and are instructed to report any adverse reactions to the research team immediately. Additionally, they are advised to consult with their healthcare practitioner for any issues related to other medications or treatments they are undergoing.

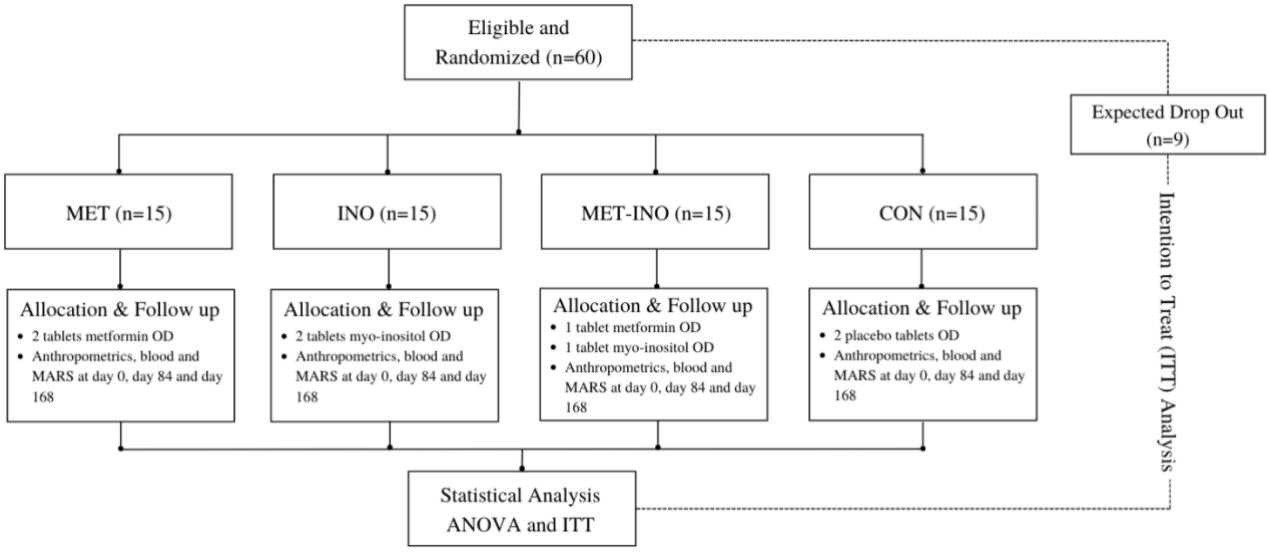

Figure 1. Flow chart of research protocol. Abbreviations used: MET (metformin treatment), INO (inositol treatment), MET-INO (combined metformin and inositol treatment), CON (placebo-control), OD (once daily), MARS (Medication Adherence Rating Scale), ANOVA (Analysis of Variance), ITT (Intention to Treat Analysis). Figure was created using the online design software Canva.

Statistical Analysis

Calculated values included BMI and HOMA-IR: BMI = mass (kg) / height² (m²); HOMA-IR = [(glucose in mg/dL × 0.05551) × insulin in μU/mL]/22.5. Multivariable analysis of variance (ANOVA) is used to identify statistically significant differences between pre- and post-intervention measurements for the assessed outcomes. An intention to treat analysis is conducted, and any missing data is accounted for using multiple imputations. Post-hoc tests are performed where necessary, and statistical significance is determined at a level of $p<0.05$.

Results

The combination of MI and metformin has not been extensively studied, but it is hypothesized that the combination therapy will result in significant improvements in insulin sensitivity compared to either treatment alone. The study aims to evaluate the effects of MI, metformin, and the combination therapy on BMI, LH:FSH ratio, and HOMA-IR values in women with PCOS. It is expected that all three intervention groups will demonstrate improved insulin sensitivity, with the combination therapy resulting in the greatest improvement.

The study includes 60 women who meet selection criteria, and an intention to treat analysis is conducted. As the research protocol is designed to avoid substantial lifestyle changes, the expected rate of dropouts is estimated to be about 15%. It is anticipated that most participants would report 20 or above on the MARS questionnaire, indicating well adherence to the study protocol. To ensure an even distribution of participants across the four groups, a randomization process is used to assign 15 participants to each group (MET, INO, MET-INO and CON).

MET:

In MET, there is anticipated improvement in insulin sensitivity, leading to a reduction in BMI, LH:FSH ratio, and HOMA-IR. It is expected that MET will experience a decrease in BMI by 2-3%, a decrease in LH:FSH ratio by 20-30%, and a decrease in HOMA-IR by 0.5-1.5 after the six-month period.

INO:

In INO, a significant improvement in insulin sensitivity is anticipated, leading to a decrease in BMI, LH:FSH ratio, and HOMA-IR. It is expected that INO will experience a decrease in BMI by 1-2%, a decrease in LH:FSH ratio by 10-20%, and a decrease in HOMA-IR by 0.2-0.4 after the six-month period.

MET-INO:

In MET-INO, a significant improvement in insulin sensitivity compared to the groups receiving either treatment alone is anticipated. It is expected that MET-INO will experience a decrease in BMI by 3-4%, a decrease in LH:FSH ratio by 30-40%, and a decrease in HOMA-IR by 1-1.5 after the six-month period.

CON:

In CON, it is expected that there will be little to no improvement in insulin sensitivity, BMI, LH:FSH ratio, or HOMA-IR values.

Discussion

PCOS is a multifaceted endocrinological condition that is managed with symptom management therapies. A key goal of these treatments is to improve insulin sensitivity, which can help regulate menstrual cycles, ovulation, reduce excess androgen levels and lower BMI. In this study, the objectives are to evaluate the effects of MI, metformin, and a combination therapy of MI and metformin on BMI, LH:FSH ratio, and HOMA-IR values in women with PCOS. It is expected that the MET-INO group will demonstrate a significant improvement in insulin sensitivity compared to the groups receiving either metformin or inositol treatment alone.

Metformin is a commonly used pharmaceutical therapy to improve the insulin sensitivity by increasing the efficiency of glucose uptake and utilization in peripheral tissues [12]. Metformin is frequently prescribed to women with PCOS as it has been associated with various positive effects, such as improving ovulation, decreasing body weight, lowering circulating excess androgen levels, and decreasing the risk of gestational diabetes mellitus [39]. Metformin has shown to reduce IR by suppressing glucose production in the liver and increasing gastrointestinal glucose absorption [12]. It prevents the production of glucagon, and inhibits certain mitochondrial complexes in hepatocytes, thereby preventing gluconeogenesis [12,18]. However, metformin has also been linked with severe gastrointestinal adverse effects, which can result in medication cessation [43]. To minimize adverse effects, a gradual increase in dosage, initially at 500 mg per day to a median of 1500 mg is recommended [39]. Metformin should be taken with meals to lessen the possibility of stomach or intestinal adverse effects during the first few weeks of therapy [41]. Studies have shown that women with PCOS who were treated with metformin for six months experienced a significant reduction in BMI [17]. It is anticipated that MET will experience a decrease in BMI by 2-3%. While metformin is generally associated with a modest reduction in BMI in women with PCOS [21], some studies have yielded inconclusive findings on its effect on BMI, though potential beneficial effects have been suggested in women with PCOS [22]. Metformin has also been shown to reduce the LH:FSH ratio in women with PCOS by improving insulin sensitivity. This effect is likely due to the ability of metformin to reduce IR, which in turn can lead to a reduction in androgen levels and an improvement in ovarian function [29]. This is consistent with studies that have found metformin to reduce LH levels in women with PCOS [28,29], with one study reporting a 23% decrease in LH levels [22]. As such, it is anticipated that MET will experience a decrease in LH:FSH ratio by 20-30%. Lastly, it is expected that metformin will lead to a decrease in HOMA-IR by 0.5-1.5. A systematic review and meta-analysis of randomized controlled trials showed that metformin significantly decreased HOMA-IR in women with PCOS [40], which is consistent with the anticipated reduction of HOMA-IR in metformin-treated patients.

MI and DCI are inositol isomers that have been evaluated to improve insulin sensitivity, enhance ovarian function, and decrease excess androgen levels in PCOS [14,23]. Women with PCOS have an altered inositol metabolism, which may contribute to the development of IR and other symptoms of the disorder [23]. Studies on the effectiveness of each compound on LH:FSH ratio regulation and insulin sensitivity have shown that MI yields the most significant improvements in women with PCOS due to its increased affinity to insulin-regulated glucose transporters, known as GLUT-4 transporters [19]. MI stimulates the translocation of these transporters to the cell membrane, thus improving IR [16]. Additionally, MI can regulate FSH signaling by reducing circulating androgen levels in the blood and increasing the sensitivity of the ovaries to gonadotropins LH and FSH [15]. Furthermore, MI is generally considered safe and well-tolerated, with few mild gastrointestinal adverse effects reported, such as nausea, bloating, and diarrhea [23,30]. The recommended dosage of MI varies by individual, but a baseline of 2000-4000 mg per day for at least 12 weeks is suggested to improve IR and other clinical symptoms of PCOS [16,25,26]. Several studies have shown that MI can influence BMI in women with PCOS [23,24]. A meta-analysis indicated that inositol supplementation was associated with a significant decrease in BMI [19]. Therefore, it is expected that INO will experience a decrease in BMI by 1-2%. A decrease in LH:FSH ratio by 10-20% is also expected in INO. While some studies have not found significant effects of MI on LH levels in women with PCOS [30,31], other studies have suggested that MI may have a beneficial effect on LH levels [19,32]. One study found that MI supplementation led to a significant reduction in LH levels in women with PCOS [42], and a randomized controlled trial reported a significant decrease in LH:FSH ratio in women with PCOS after 12 weeks of MI supplementation [24]. MI has also been found to improve HOMA-IR in women with PCOS [23,25]. It is expected that INO will experience a decrease in HOMA-IR by 0.2-0.4 after the six-month period. It has been found that MI significantly improves HOMA-IR in women with PCOS [19]. In addition, women with PCOS who were treated with MI experienced a significant improvement in glucose tolerance [35]. Overall, MI appears to be a promising therapy for improving insulin sensitivity, LH:FSH ratio, and BMI in women with PCOS.

Although several studies have compared the effects of MI and metformin on IR in women with PCOS, there is limited research on the effects of combinatory therapy. It is anticipated that the combination of metformin and MI will result in a significant decrease in BMI by 3-4%. A study that investigated the effects of combining MI and metformin in overweight women with PCOS found that participants who received both MI and metformin had an

average reduction of 4% in BMI compared to the other groups [35]. Moreover, it is expected that MET-INO will lead to a substantial decrease in the ratio of LH:FSH by 30-40%. The combination therapy of MI and metformin has been shown to significantly impact LH levels in women with PCOS, with some studies suggesting that the combination therapy may be more effective in reducing LH levels than MI alone [33]. These findings suggest that combination therapy of MI and metformin may offer an effective treatment option for improving LH levels in women with PCOS. Finally, it is anticipated that MET-INO will lead to a significant improvement in IR, with a decrease in HOMA-IR by 1-1.5 after a six-month period. Research has shown that the combination therapy of MI and metformin leads to a significant improvement in HOMA-IR compared to either treatment alone in women with PCOS [35]. Overall, studies suggest that both metformin and MI can improve IR in women with PCOS, and combination therapy may offer a more effective treatment option for improving IR in these patients.

Although this study provides valuable insights into the efficacy of metformin and MI, it is important to acknowledge its limitations and strengths. A limitation of this study is the small sample size of participants given the challenges of recruiting women diagnosed with PCOS, however, it is important to note that having a smaller sample size is acceptable in studies that involve rare conditions, such as PCOS, and given the feasibility and resource constraints. Additionally, this study focuses on the short-term effects of PCOS treatments for IR. The long-term effects of the combined treatment approach were not assessed, and future studies should investigate the effects of each treatment over time and their tolerability. A strength of this study is the avoidance of substantial lifestyle changes in the research protocol. Participants were given a MARS questionnaire to complete at assessment stages. It consists of five items, each scored on a five-point Likert scale, with a total score range of 5 to 25. Because of the protocol design, it is anticipated that most participants would report 20 or above on the scale, indicating well adherence. This study provides insight on the efficacy of alternative therapies for IR in women with PCOS beyond the conventional pharmacological treatments. The findings of this study can offer valuable information to clinicians regarding disease management and treatment options.

Conclusions

In this study, the effects of metformin, MI, and a combination therapy of metformin and MI on BMI, LH:FSH ratio, and HOMA-IR values in women with PCOS were evaluated. The combination therapy of metformin and MI is anticipated to be more effective in improving insulin sensitivity than either treatment alone. These findings have important implications for patients and clinicians managing PCOS and suggest that the combination therapy of metformin and MI may offer a more effective treatment option for improving insulin sensitivity in women with PCOS. Future research should investigate the effectiveness of the combination therapy in larger and diverse populations. It is also important to assess the long-term effects and impact of these treatments on other aspects of PCOS, such as fertility and cardiovascular risk factors.

List of Abbreviations Used

PCOS: polycystic ovary syndrome
IR: insulin resistance
MI: myo-inositol
DCI: D-chiro-inositol
BMI: body mass index
HOMA-IR: homeostatic model assessment of insulin resistance
LH: luteinizing hormone
FSH: follicle stimulating hormone
GnRH: gonadotrophin-releasing hormone
MET: metformin treatment
INO: inositol treatment
MET-INO: combined metformin and inositol treatment
CON: placebo-control
MARS: medication adherence rating scale
ANOVA: analysis of variance
ITT: intention to treat analysis

Conflicts of Interest

The authors declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This study did not require ethics approval and/or participant consent as it is a research protocol, and no participants were involved in the creation of the results.

Authors' Contributions

NA: made contributions to the design of the study, drafted the manuscript, and gave final approval of the version to be published.
MY: made contributions to the design of the study, critically revised the manuscript and gave final approval of the version to be published.
AD: made contributions to the design of the study, critically revised the manuscript and gave final approval of the version to be published.

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References

[1] Lujan ME, Chizen DR, Pierson RA. Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies. Journal of Obstetrics and Gynaecology Canada 2008 Feb;30(8):671–679. https://doi.org/10.1016/s1701-2163(16)32915-2

[2] Franks S, McCarthy MI, Hardy K. Development of polycystic ovary syndrome: involvement of genetic and environmental factors. International Journal of Andrology 2006 Feb;29(1):278–285. https://doi.org/10.1111/j.1365-2605.2005.00623.x

[3] Adams J, Polson DW, Abdulwahid N, et al. Multifollicular Ovaries: Clinical and Endocrine Features and Response to Pulsatile Gonadotropin Releasing Hormone. The Lancet 1985 Dec;326(8469-8470):1375–1379. https://doi.org/10.1016/s0140-6736(85)92552-8

[4] Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Human Reproduction 2004 Jan;19(1):41–47. https://doi.org/10.1093/humrep/deh098

[5] Azziz R, Carmina E, Dewailly D, et al. Criteria for Defining Polycystic Ovary Syndrome as a Predominantly Hyperandrogenic Syndrome: An Androgen Excess Society Guideline. The Journal of Clinical Endocrinology & Metabolism 2006 Nov;91(11):4237–4245. https://doi.org/10.1210/jc.2006-0178

[6] Rojas J, Chávez M, Olivar L, et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. International Journal of Reproductive Medicine 2014 Jan;2014:1–17. https://doi.org/10.1155/2014/719050

[7] Zeng X, Xie Y, Liu Y, et al. Polycystic ovarian syndrome: Correlation between hyperandrogenism, insulin resistance and obesity. Clinica Chimica Acta 2020 Nov;502:214–221. https://doi.org/10.1016/j.cca.2019.11.003

[8] Dunaif A. Insulin Resistance and the Polycystic Ovary Syndrome: Mechanism and Implications for Pathogenesis*. Endocrine Reviews 1997 Dec;18(6):774–800. https://doi.org/10.1210/edrv.18.6.0318

[9] Rojas J, Chávez M, Olivar L, et al. Polycystic Ovary Syndrome, Insulin Resistance, and Obesity: Navigating the Pathophysiologic Labyrinth. International Journal of Reproductive Medicine 2014 Jan;2014:1–17. https://doi.org/10.1155/2014/719050

[10] Saadia Z. Follicle Stimulating Hormone (LH: FSH) Ratio in Polycystic Ovary Syndrome (PCOS) - Obese vs. Non- Obese Women. Medical Archives 2020 Aug;74(4):289. https://doi.org/10.5455/medarh.2020.74.289-293

[11] Rebar R, Judd HL, Yen SS, et al. Characterization of the inappropriate gonadotropin secretion in polycystic ovary syndrome. Journal of Clinical Investigation 1976 May;57(5):1320–1329. https://doi.org/10.1172/jci108400

[12] Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia 2017 Aug;60(9):1577–1585. https://doi.org/10.1007/s00125-017-4342-z

[13] Baptiste CG, Battista M-C, Trottier A, et al. Insulin and hyperandrogenism in women with polycystic ovary syndrome. The Journal of Steroid Biochemistry and Molecular Biology 2010 Oct;122(1-3):42–52. https://doi.org/10.1016/j.jsbmb.2009.12.010

[14] Kalra S, Kalra B, Sharma J. The inositols and polycystic ovary syndrome. Indian Journal of Endocrinology and Metabolism 2016 Sep-Oct;20(5):720. https://doi.org/10.4103/2230-8210.189231

[15] Merviel P, James P, Bouée S, et al. Impact of myo-inositol treatment in women with polycystic ovary syndrome in assisted reproductive technologies. Reproductive Health 2021Jan;18(1). https://doi.org/10.1186/s12978-021-01073-3

[16] Unfer V, Facchinetti F, Orrù B, et al. Myo-inositol effects in women with PCOS: a meta-analysis of randomized controlled trials. Endocrine Connections 2017 Nov;6(8):647–658. https://doi.org/10.1530/ec-17-0243

[17] Lord JM. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 2003 Oct;327(7421). https://doi.org/10.1136/bmj.327.7421.951

[18] Pernicova I, Korbonits M. Metformin—mode of action and clinical implications for diabetes and cancer. Nature Reviews Endocrinology 2014 Jan;10(3):143–156. https://doi.org/10.1038/nrendo.2013.256

[19] Unfer V, Carlomagno G, Dante G, et al. Effects of Myo-Inositol in Women with PCOS: A Systematic Review of Randomized Controlled Trials. Gynecological Endocrinology 2012 Feb; 28(7): 509-515. https://doi.org/10.3109/09513590.2011.650660

[20] Barber TM, Hanson P, Weickert MO, et al. Obesity and Polycystic Ovary Syndrome: Implications for Pathogenesis and Novel Management Strategies. Clinical Medicine Insights: Reproductive Health 2019 Sep;13:117955811987404. https://doi.org/10.1177/1179558119874042

[21] Palomba S, Falbo A, Carrillo L, et al. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertility and Sterility 2011 Oct;96(6):1384-1390.e4. https://doi.org/10.1016/j.fertnstert.2011.09.020

[22] Guan Y, Wang D, Bu H, et al. The Effect of Metformin on Polycystic Ovary Syndrome in Overweight Women: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. International Journal of Endocrinology 2020 Sep;2020:1–12. https://doi.org/10.1155/2020/5150684

[23] Nordio M;Proietti E. The combined therapy with myo-inositol and D-chiro-inositol reduces the risk of metabolic disease in PCOS overweight patients compared to myo-inositol supplementation alone. European review for medical and pharmacological sciences 2012 May;16(5): 575-81. https://pubmed.ncbi.nlm.nih.gov/22774396/

[24] Artini PG, Di Berardino OM, Papini F, et al. Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study. Gynecological Endocrinology 2013 Jan;29(4):375–379. https://doi.org/10.3109/09513590.2012.743020

[25] Genazzani AD, Lanzoni C, Ricchieri F, et al. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecological Endocrinology 2009 Jul;24(3):139–144. https://doi.org/10.1080/09513590801893232

[26] Costantino D. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. European review for medical and pharmacological sciences 2009 Mar-Apr;13(2): 105-110. https://pubmed.ncbi.nlm.nih.gov/19499845/

[27] Palomba S, Orio F, Falbo A, et al. Prospective Parallel Randomized, Double-Blind, Double-Dummy Controlled Clinical Trial Comparing Clomiphene Citrate and Metformin as the First-Line Treatment for Ovulation Induction in Nonobese Anovulatory Women with Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology & Metabolism 2005 Jul;90(7):4068–4074. https://doi.org/10.1210/jc.2005-0110

[28] Morin-Papunen LC, Koivunen RM, Ruokonen A, et al. Metformin therapy improves the menstrual pattern with minimal endocrine and metabolic effects in women with polycystic ovary syndrome. Fertility and Sterility 1998 Apr;69(4):691–696. https://doi.org/10.1016/s0015-0282(98)00011-9

[29] Oride A, Kanasaki H, Purwana IN, et al. Effects of metformin administration on plasma gonadotropin levels in women with infertility, with an in vitro study of the direct effects on the pituitary gonadotrophs. Pituitary 2010 Feb;13(3):236–241. https://doi.org/10.1007/s11102-010-0223-x

[30] Gerli S. Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. European review for medical and pharmacological sciences 2011 Sept-Oct;11(5). https://pubmed.ncbi.nlm.nih.gov/18074942/

[31] Pizzo A, Laganà AS, Barbaro L. Comparison between effects of myo-inositol andd-chiro-inositol on ovarian function and metabolic factors in women with PCOS. Gynecological Endocrinology 2013 Dec;30(3):205–208. https://doi.org/10.3109/09513590.2013.860120

[32] Ciotta. Effects of myo-inositol supplementation on oocyte's quality in PCOS patients: A double blind trial. European review for medical and pharmacological sciences 2018 May;15(5). https://pubmed.ncbi.nlm.nih.gov/21744744/

[33] Krysiak R, Kowalcze K, Okopień B. Myo-Inositol Enhances the Inhibitory Effect of Metformin on Gonadotropin Levels in Postmenopausal Women. Gynecologic and Obstetric Investigation 2022 Jan;87(6):373–380. https://doi.org/10.1159/000527365

[34] Jensterle M, Kravos NA, Ferjan S, et al. Long-term efficacy of metformin in overweight-obese PCOS: longitudinal follow-up of retrospective cohort. Endocrine Connections 2020 Jan;9(1):44–54. https://doi.org/10.1530/ec-19-0449

[35] Genazzani AD, Santagni S, Rattighieri E, et al. Modulatory role of D-chiro-inositol (DCI) on LH and insulin secretion in obese PCOS patients. Gynecological Endocrinology 2014 Dec;30(6):438–443. https://doi.org/10.3109/09513590.2014.897321.

[36] Wallace TM, Levy JC, Matthews DR. Use and Abuse of HOMA Modeling. Diabetes Care 2004 Jun;27(6):1487–1495. https://doi.org/10.2337/diacare.27.6.1487

[37] Cassar S, Misso ML, Hopkins WG, et al. Insulin resistance in polycystic ovary syndrome: a systematic review and meta-analysis of euglycaemic–hyperinsulinaemic clamp studies. Human Reproduction 2016 Oct;31(11):2619–2631. https://doi.org/10.1093/humrep/dew243

[38] Vassilatou E. Nonalcoholic fatty liver disease and polycystic ovary syndrome. World Journal of Gastroenterology 2014 Jul;20(26):8351. https://doi.org/10.3748/wjg.v20.i26.8351

[39] Lashen H. Review: Role of metformin in the management of polycystic ovary syndrome. Therapeutic Advances in Endocrinology and Metabolism 2010 Aug;1(3):117–128. https://doi.org/10.1177/2042018810380215

[40] Teede HJ, Misso ML, Costello MF, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome†‡. Human Reproduction 2018 Sept;33(9):1602–1618. https://doi.org/10.1093/humrep/dey256

[41] Bonnet F, Scheen A. Understanding and overcoming metformin gastrointestinal intolerance. Diabetes, Obesity and Metabolism. 2017 Apr 22;19(4):473–81. https://doi.org/10.1111/dom.12854

[42] Dinicola S, Chiu TTY, Unfer V, et al. The rationale of the myo-inositol and D-chiro-inositol combined treatment for polycystic ovary syndrome. The Journal of Clinical Pharmacology 2007 Sept-Oct;54(10):1079–1092. https://doi.org/10.1002/jcph.362

[43] McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia 2016 Jan 6 ;59(3):426–435. https://doi.org/10.1007/s00125-015-3844-9

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