UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

The Effects of Metformin and Myo-Inositol on Hyperandrogenism, Insulin Sensitivity, and Fertility in Polycystic Ovary Syndrome: A Literature Review

Garene A. Matossian [1]*, Isabella M. Buklarewicz [1], Vaneeza A. Moosa [1]

[1] Department of Human Biology, University of Toronto, Toronto, Ontario, Canada M5S 3H3

*Corresponding Author: garene.matossian@mail.utoronto.ca

Abstract

Introduction: Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder that occurs due to a hormone imbalance in the ovaries. It can cause the development of fluid-filled cysts on the follicles, causing infertility. Further, PCOS can cause insulin resistance and hyperandrogenism, increasing the amount of glucose and testosterone levels in the body. As a result, PCOS symptoms could include irregular or absent periods, weight gain, hirsutism, and more. PCOS patients are also at higher risk of developing type 2 diabetes, depression, and high blood pressure. Currently, there are no cures for PCOS, but it can be managed with lifestyle changes, contraceptive pills for irregular periods, and fertility treatments. Two of these treatments include inositol and metformin. The objective of the study is to ascertain how these therapies affect PCOS symptoms such as hyperandrogenism, insulin sensitivity, and infertility.

Methods: Primary articles were found through the PubMed and OVID-Medline databases to investigate the effect of inositol or metformin on PCOS. Keywords such as PCOS, inositol, metformin, myo-inositol, insulin sensitivity, androgens, and fertility were used. Research published before 2010 was excluded.

Results: The results found that metformin and inositol decreased the amounts of free testosterone and glucose in women with PCOS. Further, oocyte quality and production were improved in women taking metformin and inositol. These results were seen in women of all ages and of all BMIs.

Discussion: Both metformin and MI are shown to significantly improve PCOS symptoms of hyperandrogenism, insulin sensitivity, and fertility issues. Although some limitations were present within the review and the studies examined due to exclusions, the review presents a comprehensive outlook on the impact of the interventions mentioned. Establishing a foundation for clinical trials would allow for the integration of these interventions into healthcare settings.

Conclusion: A combination of both metformin and inositol, as well as diet and lifestyle changes can significantly improve the symptoms and life quality of individuals with PCOS. Future research would benefit from further studies done into investigating the combined effects of metformin and MI, as well as further assessment of secondary symptoms, as well as regarding the dosage of myo-inositol and metformin.

Keywords: PCOS; metformin; myo-inositol; inositol; insulin sensitivity; insulin resistance; hyperandrogenism; androgens; fertility

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine-reproductive-metabolic disorder that affects an estimated 5-15% of reproductive-aged women globally [1]. The symptoms of PCOS are highly variable; some common symptoms include hyperandrogenism, the presence of ovarian cysts, and irregular menstrual cycles [1,2]. Subsequently, acne, hirsutism, insulin resistance, and infertility may be experienced [1,2].

Diagnosing PCOS is challenging due to its diverse symptomology. Though there is no diagnostic test for PCOS, the Rotterdam criteria can be used [3]. According to these criteria, an individual must have two of the following three symptoms: hyperandrogenism, irregular menses, or abnormal ovarian morphology [2,4]. It is important to note that age, ethnicity, race, and lifestyle factors must also be considered when diagnosing PCOS [5].

PCOS management encompasses a range of strategies and treatments. Lifestyle factors including exercise and diet changes have been shown to manage symptoms of PCOS, and are among the first line of treatment [5]. These changes can lead to weight loss, which has been shown to reduce PCOS characteristics, including insulin sensitivity and irregular menses [5]. Current research suggests a diet moderate in carbohydrates and fats, and high in fiber and protein sources to improve the health of women with PCOS [5]. Medications acting on hormones, including estro-progestins, and insulin sensitizers, are commonly used to treat PCOS symptoms [7,8]. Insulin sensitizers, specifically, decrease the body's resistance to insulin - a

common symptom in PCOS. This is crucial, because insulin resistance in PCOS has various pathophysiological implications, including increased androgen production, hyperinsulinemia, and ovulation disruption [5]. Due to their pathophysiological effects, insulin sensitizers have also shown promising outcomes in managing infertility, as observed in several studies.

Aside from insulin sensitizers, certain progestins have been shown to exhibit antiandrogen properties, broadening the range of treatment options. Hirtuism, caused by hyperandrogenism, is often managed through cosmetic procedures such as laser hair removal or hair growth treatments [7,8]. Overall, there are a range of therapeutic options available to manage the various symptoms of PCOS, and their effectiveness can be optimized by tailoring them to individual patient needs [6].

This range of treatment options available for PCOS offers promising outcomes in managing its various symptoms. Two of these PCOS-managing treatments could include metformin and myo-inositol.

Metformin is a well-established prescription insulin sensitizer used to manage PCOS symptoms, such as hirsutism, menstrual irregularities, and infertility [9]. Its mechanism of action involves reducing hepatic glucose production, improving insulin sensitivity, and reducing glucose absorption from the gut, which ultimately leads to a decrease in elevated insulin levels [10]. This is particularly relevant to the pathogenesis of PCOS as insulin resistance is a common hallmark, contributing to its various manifestations. In addition to improving insulin sensitivity, metformin has been demonstrated to lower androgen levels and increase ovulation rates, making it a valuable therapeutic option for women with PCOS who are attempting to conceive [11]. Metformin also regulates menstrual cycles and promotes ovulation, which leads to higher clinical pregnancy rates [11–14]

Myo-inositol (MI), a form of inositol, is a popular supplement used by women with PCOS. It is suggested to improve insulin sensitivity, reduce inflammation, and regulate hormones, thereby supporting menstrual cycle regulation, fertility, and weight management, and reducing symptoms like hirsutism and acne [15]. In women undergoing fertility treatments, MI has been shown to improve egg quality [16].

This paper aims to review the effects of metformin and MI in managing PCOS, focusing on the primary outcomes of fertility, hyperandrogenism (measured via testosterone levels in the blood), and insulin sensitivity (measured via glucose levels). Evaluating these treatments is essential in understanding their potential benefits and limitations, mechanisms of action, and interactions with other therapies and lifestyle factors. By assessing the effects of these treatments, we can better understand the pathophysiology of PCOS, which will lead to and facilitate the development of more effective therapeutic strategies.

Methods

Literature Search

To conduct this review, a search of the PubMed and OVID-Medline databases was done using specific keywords such as “polycystic ovary syndrome,” “PCOS,” “inositol,” “metformin,” “insulin sensitivity,” and “androgens.” The search was limited to human studies published in the English language between January 2010 and July 2023. The initial step involved collecting and independently reviewing articles to determine their eligibility for the study. The eligible studies were assessed by three independent reviewers by analyzing the titles and abstracts and then the full text.

Table 1. Search Process.

Databases	Search Terms	Inclusion Criteria	Date Range	Language
PubMed OVID-Medline	“polycystic ovary syndrome” OR “PCOS” AND “inositol” OR “metformin” OR “insulin sensitivity” OR “androgens” OR “myo-inositol” OR “hyperandrogenism: OR “fertility” OR “infertility”	Human studies, English language	January 2010-July 2023	English

Study Selection Criteria

The inclusion criteria were randomized controlled trials that assessed the efficacy and safety of inositol and/or metformin in women with PCOS. The age range selected was adults (>+19). Dosage was also evaluated, along with BMI presented and any significant life events (such as pregnancy). Outcome measures were evaluated, with a focus on primary symptoms including fertility, hyperandrogenism (testosterone levels via blood), and insulin sensitivity (glucose). Secondary outcomes included DHEA, oxidative stress of follicular fluid, weight, and hirsutism.

Data Extraction and Statistical Analysis

The data extracted included the study design, sample size, intervention, outcome measures, significant findings, and adverse events (seen in Fig. 1). The statistical methods used in each article were evaluated for their consistency and accuracy. The Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for

observational studies were used to assess the risk of bias. If the p-value was <0.05, the differences were considered to be statistically significant.

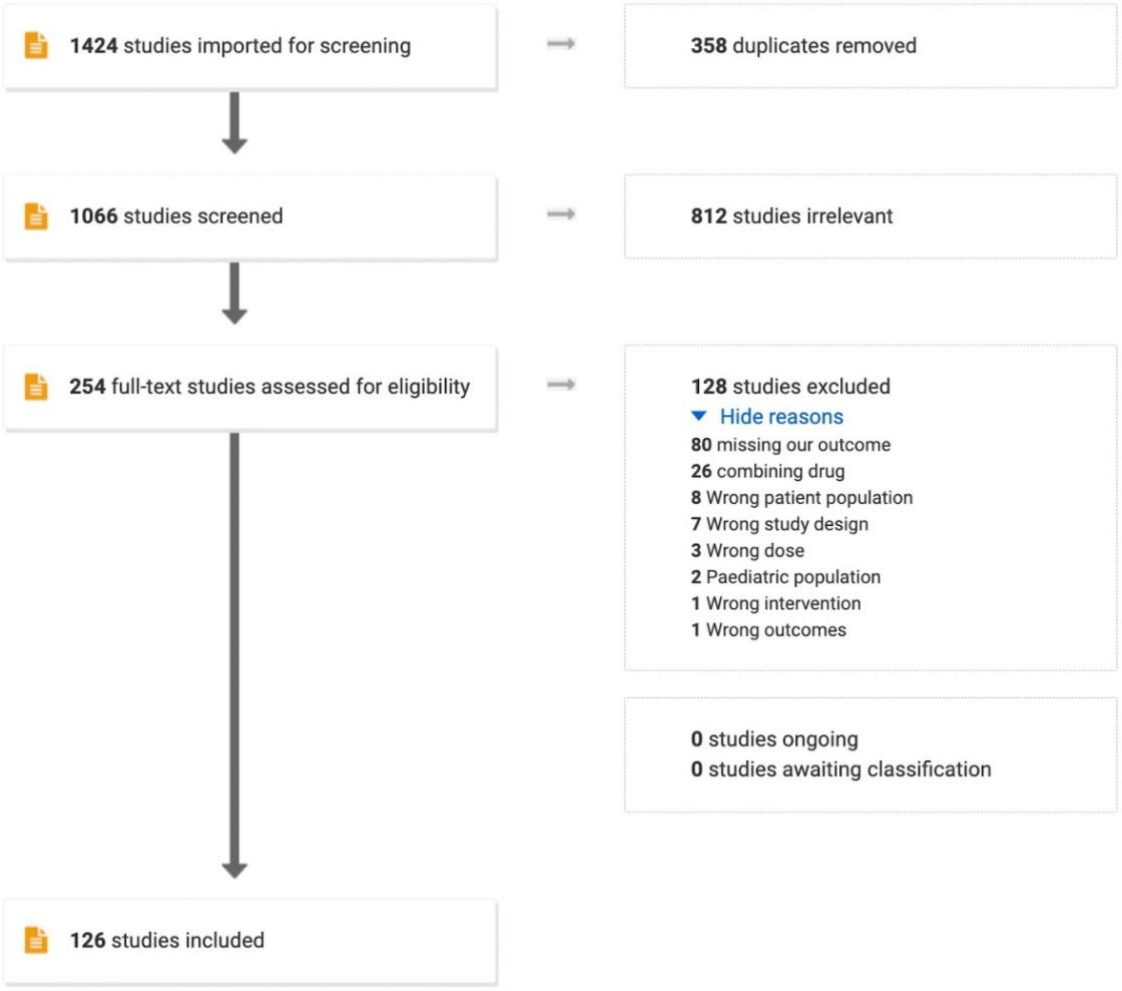

Figure 1. Flowchart of Data Extraction (Covidence.com).

Results

A total of 10 articles that evaluate the effects of metformin and MI on PCOS were included in this review, with a focus on major outcomes of fertility, hyperandrogenism, and insulin sensitivity. Metformin considerably improved insulin sensitivity and had a beneficial effect on hyperandrogenism and metabolic changes when paired with lifestyle adjustments. MI was demonstrated to improve ovarian blood flow and oocyte quality in women undergoing ovulation induction for intracytoplasmic sperm injection (ICSI). The results suggest that metformin and Ml can be effective therapies for PCOS, especially when paired with lifestyle changes. However, the effects may differ depending on individual BMI and other variables (Table 2).

Metformin

Insulin Sensitivity

The results of the three studies reviewed suggest that metformin may effectively improve insulin sensitivity in women with PCOS [17–19]. The present study aimed to investigate the effects of metformin on insulin sensitivity in women with PCOS, and to evaluate whether the dose and BMI of the patients have an impact on the outcomes. In a randomized controlled trial conducted by Fruzetti et al. [14], 50 women with a BMI greater than or equal to 25 kg/m2 and HOMA-IR >2.5 were included. Participants who received metformin experienced a significant decrease in BMI and AUC insulin, indicating enhanced insulin sensitivity. This is consistent with the findings of Luque-Ramurez et al. [18], who investigated the effects of metformin on insulin sensitivity in women with PCOS, along with

hyperandrogenism and ovulatory dysfunction. The study included 34 participants randomly placed into two groups, one receiving metformin and the other an oral contraceptive. Findings indicated that metformin is significantly associated with improved insulin sensitivity compared to participants that received birth control and the control group.

On the other hand, some studies did not find significant results. Yasmin et al [19] conducted a randomized controlled trial to examine the effects of increasing the dose of metformin on insulin sensitivity and androgens in individuals with PCOS. The study included 40 participants, divided into groups depending on their BMI, a distinction that was also made by Fruzetti et al. [17]. The results showed a trend of reduced hyperandrogenism, but only one group showed a significant improvement. There was also a trend of reduction of fasting insulin, but only one group reduced their fasting insulin concentration significantly.

Hyperandrogenism

Hyperandrogenism was also a primary outcome measured. Significantly improved effects were observed for hyperandrogenism: Otta et al. [20] conducted a study where 30 women with PCOS were randomly assigned to receive either metformin or a placebo for a period of four months. All participants underwent lifestyle modifications. The results showed that women who received metformin had a significant reduction in serum testosterone levels and a decrease in insulin sensitivity. Additionally, the menstrual cycle of participants was tracked throughout the study, and it was observed that metformin improved menstrual regularity in women with PCOS.

Victor et al. [21] conducted a similar to Otta et al. [20], which included a randomized controlled trial where 40 women with PCOS and 44 control participants were included in the study. Here, the study analyzed fasting glucose and androstenedione levels rather than insulin sensitivity as in Otta et al. [20]. The women with PCOS received metformin, while the control group did not. The study found that women with PCOS who received metformin experienced a reduction in fasting glucose levels and androstenedione levels.

Both Otta et al. [20] and Victor et al.'s [21] studies indicate that metformin may be useful in lowering serum testosterone levels and enhancing menstrual regularity in women with PCOS. According to Otta et al.'s study, women who were prescribed metformin experienced a significant decrease in serum testosterone levels and insulin sensitivity, which could potentially ameliorate PCOS symptoms. In addition, Otta et al. [20] found that metformin enhanced menstrual regularity in women with PCOS. Similarly, Victor et al. [21] described that women with PCOS who received metformin had lower androstenedione levels, which could help with PCOS symptoms. Overall, these findings indicate that metformin may be a viable therapy choice for women with PCOS.

Inositol

Fertility

Fertility is another outcome often measured in individuals with PCOS, with significant improvement seen. Ozay et al. [22] investigated the effects of inositol on ovarian blood flow, while Unfer et al studied the effects of two different forms of inositol (MI), and d-chiro-inositol (DCI), on oocyte quality. The latter study was a randomized controlled trial that involved women with euglycemic PCOS undergoing ovulation induction for ICSI. The participants were assigned to take MI or DCI for 12 months. The results indicated that women in the MI group had a higher number of MII oocytes, fewer immature oocytes, and more embryo grade 1 than those in the DCI group. Furthermore, women who took MI had a significantly higher rate of successful pregnancies. Specifically, the study found that MI was more effective than DCI and that MI can significantly improve fertility outcomes in women with euglycemic PCOS. Overall, these studies shed light on the potential benefits of inositol for women with PCOS, with one study suggesting improvements in ovarian blood flow and another indicating improved oocyte quality and pregnancy outcomes.

Ozay et al. [22] and Unfer et al.'s [15] studies imply that inositol may benefit women with PCOS. Ozay et al. [22] discovered that inositol increased ovarian blood flow, but Unfer et al observed that MI was more effective than DCI in enhancing oocyte quality and pregnancy outcomes in women with euglycemic PCOS undergoing ovulation induction for ICSI. MI was linked to a higher number of MII oocytes, less immature oocytes, more embryo grade 1 embryos, and a considerably higher likelihood of successful pregnancies. These data imply that inositol, particularly MI, can be a useful supplement for PCOS women undergoing reproductive treatments.

Metformin vs. Inositol

Metformin and inositol have often been compared in terms of significant outcomes for individuals with PCOS, with both being found to be beneficial for different outcomes, dependent on the individual's characteristics. One study conducted by Tagliaferri et al. [23] compared the effects of metformin and MI on obese women with PCOS. This randomized controlled trial involved 34 women with a mean age of 25-62 years and a BMI of 32-55 kg/m2. The women were randomly assigned to one of the medications for 6 months, followed by a 3-month washout period, and then switched to the other medication for another 6 months. The results showed that both drugs reduced insulin response to an oral glucose tolerance test (OGTT) and improved insulin sensitivity. However, metformin had more significant effects on metabolic factors such as body weight, menstrual pattern, LH and estradiol levels, and androgen and anti-Mullerian hormone levels, while MI did not show the same changes.

To study changes to glucose and testosterone levels, Soldat-Stanković et al. [24] conducted a randomized control trial involving 66 participants with PCOS, aged 18-40 years, and with normal weight and overweight/obesity. The participants received either metformin or MI for 6 months. The results showed that metformin had a greater effect on reducing glucose levels, with participants on metformin having lower AUC glucose and fasting glucose levels than those on MI. In contrast, participants on MI had higher testosterone levels than those on metformin, which is similar to the findings of the study by Tagliaferri et al. [23].

To study insulin resistance, Shokrpour et al.[25] also compared the effects of metformin and MI, but in a study involving fewer participants: 53 women with PCOS aged 18-40 years. The participants were randomly assigned to either take metformin or MI, like Soldat-Stanković et al. [24]. The results showed that participants who took MI had lower fasting plasma glucose levels, lower serum insulin levels, and lower insulin resistance as measured by the HOMA-IR. On the other hand, participants who took metformin exhibited no significant change in these factors.

While different results are seen in the studies, the benefits of metformin and inositol vary depending on the outcomes observed. Metformin has more significant improvements in hyperandrogenism and metabolic factors, while inositol seems to improve insulin resistance.

Table 2. Summary of Examined Reviews

Study & Year	Participants (n)	Study Type	Intervention	Dose	Duration	Significant Results
Yasmin et al., 2011 [16]	40	Randomised controlled trial	Metformin	1-3g/day	2 months, increased dose every 8 weeks (total 3g increase) total 24 weeks	A slight downward trend was seen across the timeline till 24 weeks but only group with highest BMI showed a significant decline in testosterone concentration in 6 months and in fasting insulin concentration.
Victor et al., 2015 [18]	84	Randomised controlled trial	Metformin	500mg/day	12 weeks	Experimental group showed decreased glucose, FSH, androstendione, increased DHEA-S.
Unfer et al., 2011 [13]	84	Randomised controlled trial	Myo-inositol	4 g/d	12 months of IVF	MI was compared to D-chiro inositol (DCI). MI rather than DCI is able to improve oocyte and embryo quality in euglycemic PCOS patients.
Tagliaferri et al., 2017 [20]	34	Randomised controlled crossover study	Metformin and Myo-inositol (MI)	Group 1: metformin 850 mg twice a day Group 2: MI 500 mg two oral pills twice a day	6 months + 3 months washout + 6 month=15 months	Both drugs improved insulin sensitivity. Metformin decreased body weight and improved menstrual pattern (FG score). Metformin decreased LH and estradiol levels, androgen and anti-mullerian hormone levels. These changes were not seen in the MI group.

Study & Year	Participants (n)	Study Type	Intervention	Dose	Duration	Significant Results
Soldat-Stanković et al., 2022 [21]	66	Randomised controlled trial	Myo-inositol and Metformin	1500g metformin and 4g MI daily	6 months	the study showed similar effects of MET and MI on BMI, body composition, hormonal profile, glucose and insulin metabolism, and adiponectin level in PCOS women. Both insulin sensitizers were useful in reducing BMI and improving body composition without significant differences between the two treatments.
Shokrpour et al., 2019 [22]	53	Randomised controlled trial	Myo-inositol and Metformin	500mg metformin three times a day; 2g myoniositol +200mg folic acid twice a day	12 weeks	Reduction in fasting plasma glucose, serum insulin levels, insulin resistance, serume triglyceride and LDL-cholesterol in both groups
Özay et al., 2019 [19]	180	Randomised controlled trial	Myo-inositol	Group 1: received OCP with 30mg ethinyl estradiol plus 3mg drospirenone; Group 2: 4g myoinositol plus 400mg folic acid; Group 3: no intervention; Group 4-6: healthy controls receiving OPC, myoinositol, or nothing	3 months	Increase in ovaries resistance index and pulsatility index of ovarian stromal blood flow using OPC and MYO.
Luque-Ramírez et al., 2010 [15]	34	Randomised controlled trial	Metformin	850mg twice a day	24 weeks	Improvement in insulin resistance and reduction in IL-6 in people treated with metformin
Fux Otta et al., 2010 [17]	30	Randomised controlled trial	Metformin	1500mg/day	4 months	Reduction in fasting insulin, HOMA index, testosterone levels, and waist circumference in group taking metformin
Fruzzetti et al., 2017 [14]	50	Randomised controlled trial	Metformin and Myo-inositol	1500mg/day metformin; 4g/day myoinositol	6 months	Both drugs reduces BMI, normalized menstrual cycles, and improved insulin sensitvivity.

Discussion

Summary

According to the 10 papers reviewed, metformin and MI significantly alleviate PCOS symptoms in women. They can be an effective tool for the clinical therapy of PCOS and can influence BMI and insulin uptake sensitivity favorably. Further, metformin and MI are shown to improve fertility in women with PCOS and hyperandrogenism. Based on the papers reviewed in this study, both of these drugs are suitable for treating the issues of insulin sensitivity, hyperandrogenism, and fertility faced by women with PCOS.

Interpretations

Metformin

Metformin causes the liver's AMP-activated protein kinase (AMPK), an enzyme that controls lipid and glucose metabolism, to become active [24]. Once triggered, it instructs the liver to produce less glucose, bringing blood glucose levels down [24]. His leads to the reduction of insulin-resistance-associated symptoms, such as an increased BMI due to associated weight loss. Thus, previous literature also supports the findings that metformin can improve insulin sensitivity.

Additionally, metformin was also found to have significant effects on the reduction of hyperandrogenism and metabolic factors in women with PCOS The papers reviewed found that serum testosterone levels were reduced after the use of metformin, indicating improvements in hyperandrogenism [15-18] Metformin is thought to reduce serum testosterone levels by inhibiting the production of androgens in the ovaries and adrenal glands [8]. It also increases the level of sex hormone-binding globulin (SHBG), a protein that binds to androgens in the blood, reducing their activity [7,8]. These actions help to reduce the overall level of androgens in the body, leading to a reduction in symptoms of hyperandrogenism; this improves menstrual regularity in women, enhancing fertility.

Though the mechanism is not fully understood, it is thought that metformin can also inhibit androgen production in the ovaries and adrenal glands by reducing insulin levels, as well as the activity of insulin-like growth factor-1 (IGF-1) [28]. Insulin and IGF-1 both have the ability to stimulate androgen production [29]. Thus, by reducing their activity, metformin lowers androgen production and alleviates hyperandrogenism in women with PCOS. The reduction of hyperandrogenism can improve related symptoms such as hirsutism, acne, and menstrual irregularities [26,30,31]. Remarkably, metformin's effectiveness is not dose-dependent, allowing clinicians to adjust the dosage in accordance with the demands of each patient, along with side effects and efficacy. Metformin can be a practical and reasonable option for physicians as it is a generally safe and affordable medication.

Myo-Inositol

The findings of this review stating that MI improves the impact of PCOS symptoms is consistent with past literature. A previous review indicated that MI is valuable in improving ovarian blood flow and oocyte quality in individuals with PCOS (Raffone et. al. 2011). In another literature review, authors found that MI increased insulin sensitivity and decreased hyperandrogenism, in addition to enhancing oocyte and embryo quality in women with PCOS [32]. Furthermore, Ciotta et al. [33] demonstrated in a double-blind trial that MI was effective for treating PCOS patients undergoing ovulation induction due to both its ability to lower insulin and its function in oocyte maturation.

MI's involvement as a precursor of inositol phosphoglycans (IPGs), which are signaling molecules that regulate ovarian function, is one probable mechanism of action for its favorable effects on ovarian function [34]. MI supplementation may boost IPG synthesis and improve ovarian function, resulting in higher oocyte quality and blood flow, and improved contraception rates [34]. A randomized control trial found that women who were prescribed MI had a significantly greater number of oocytes, which were of high quality [33]. The study also highlighted that MI improved insulin sensitivity by stimulating the uptake of glucose, which may help to restore hormonal balance and improve oocyte quality [34]. Therefore, both this literature review, as well as previous studies, display the potential benefits of MI supplementation in improving ovarian function and oocyte quality with PCOS. However, more research is needed to understand the mechanism of action, optimal dosage and duration of treatment.

Strengths and Limitations

There are several strengths of this review paper. The studies reviewed allowed for an in-depth comparison between the use of metformin and MI in decreasing PCOS symptoms. Moreover, comparing the effects of the two drugs on specific PCOS symptoms allowed for a direct evaluation of the drug's efficiencies. Further, selecting only recent papers with specific keywords also allowed for only the most relevant papers to be reviewed.

Although the studies reviewed provide valuable insights into metformin and MI in women with PCOS, there are several limitations to be considered. First, the search was limited to only two databases, PubMed and OVID-Medline, in English, between January 2010 and July 2023. This naturally excluded other published studies that may have been relevant. Additionally, a comparison of metformin and MI with other interventions was not seen; rather the baseline group was always a placebo or control, which does not allow for a full understanding of the effectiveness of metformin or MI. Furthermore, this review did not focus on factors such as quality of life and psychological impact, which may significantly affect PCOS symptomology and presentation. Thus, it is possible that the treatments explored, metformin and MI, are not effective for these excluded symptoms. In terms of the studies, some limitations seen were the variety of the sample sizes, interventions, and outcome measures utilized, which makes comparing the results and identifying effective strategies involving metformin and MI complex.

Conclusion

Both metformin and MI are valid treatments for PCOS and have been shown to significantly improve symptoms. Combining these treatments with lifestyle changes, such as a healthy diet and regular exercise, may further enhance their effectiveness in managing PCOS. However, the exact dose-dependent and BMI-dependent effects of metformin

and MI on patients with PCOS are not yet fully understood, and further research is needed to fully understand their mechanisms of action and potential side effects.

The results discussed in this review lay the groundwork for further investigation in this field while highlighting the potential advantages of these therapies, emphasizing the need for further research to be done. The review concentrated on the main PCOS symptoms, such as hyperandrogenism, insulin sensitivity, and fertility, but neglected to mention other crucial elements like the quality of life and psychological consequences. As a result, the review's conclusions may not apply to all areas of PCOS management. Based on these findings, future directions suggested are researching the long-term effects of metformin and MI, determining optimal dosage and treatment durations, and investigating the mechanism of action of these medications to understand their effects more deeply. This would allow for a more nuanced understanding of the function and impact of these two interventions, providing a better foundation for further clinical studies and implementation into healthcare.

List of Abbreviations Used
PCOS: polycystic ovary syndrome
MI: myo-inositol
IGF-1: insulin-like growth factor-1
SHBG: sex hormone-binding globulin
IPGs: inositol phosphoglycans

Conflicts of Interest: The author(s) declare that they have no conflict of interests.

Ethics Approval and/or Participant Consent: No ethics/ participant consent was needed.

Authors' Contributions:
GAM: contributed to the conception and analysis of the review, drafted and revised the content, and gave final approval of the version to be published.
IMB: contributed to the conception and analysis of the review, drafted and revised the content, and gave final approval of the version to be published.
VAM: contributed to the conception and analysis of the review, drafted and revised the content, and gave final approval of the version to be published.

Acknowledgments: Thank you to the URNCST Team and mentor Patricia Acosta for their support.

Funding: This study was not funded.

References
[1] Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. The Journal of Clinical Endocrinology and Metabolism. 2006; 91(11):4237–45. https://doi.org/10.1210/jc.2006-0178
[2] Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: A review article. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2019;3(100060):100060. https://doi.org/10.1016/j.eurox.2019.100060
[3] Smet M-E, McLennan A. Rotterdam criteria, the end. Australasian Journal of Ultrasound in Medicine 21. 2018;21(2):59–60. https://doi.org/10.1002/ajum.12096
[4] Witchel SF, Oberfield SE, Peña AS. Polycystic ovary syndrome: Pathophysiology, presentation, and treatment with emphasis on adolescent girls. Journal of the Endocrine Society. 2019;3(8):1545–73. https://doi.org/10.1210/js.2019-00078
[5] Kshetrimayum C, Sharma A, Mishra VV, Kumar S. Polycystic ovarian syndrome: Environmental/ occupational, lifestyle factors; an overview. Journal of the Turkish German Gynecological Association. 2019; 20(4):255–63. https://doi.org/10.4274/jtgga.galenos.2019.2018.0142
[6] Rashid R, Mir SA, Kareem O, Ali T, Ara R, Malik A, et al. Polycystic ovarian syndrome-current pharmacotherapy and clinical implications.Taiwanese Journal of Obstetrics & Gynecology. 2022;61(1):40–50. https://doi.org/10.1016/j.tjog.2021.11.009
[7] Vrbíková J, Cibula D. Combined oral contraceptives in the treatment of polycystic ovary syndrome. Human Reproduction Update. 2005;11(3):277–91. https://doi.org/10.1093/humupd/dmi005
[8] Pasquali R. Contemporary approaches to the management of polycystic ovary syndrome. Therapeutic Advances in Endocrinology and Metabolism. 2018;9(4):123–34. https://doi.org/10.1177/2042018818756790
[9] Radosh L. Drug treatments for polycystic ovary syndrome. American Family Physician. 2009;79(8): 671–6. https://pubmed.ncbi.nlm.nih.gov/19405411/
[10] Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577–85. https://doi.org/10.1007/s00125-017-4342-z
[11] Pasquali R, Gambineri A. Targeting insulin sensitivity in the treatment of polycystic ovary syndrome. Expert Opinion on Therapeutic Target. 2009;13(10):1205–26. https://doi.org/10.1517/14728220903190699

[12] Pasquali R, Stener-Victorin E, Yildiz BO, Duleba AJ, Hoeger K, Mason H, et al. PCOS Forum: research in polycystic ovary syndrome today and tomorrow: Forum in PCOS research. Clinical Endocrinology (Oxf). 2011;74(4):424–33. https://doi.org/10.1111/j.1365-2265.2010.03956.x

[13] Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligo amenorrhoea and subfertility. Cochrane Database of Systematic Reviews. 2010;(1):CD003053. https://doi.org/10.1002/14651858.CD003053.pub4

[14] Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. Endocrine Reviews. 2009;30(1):1–50. https://doi.org/10.1210/er.2008-0030

[15] Unfer V, Carlomagno G, Dante G, Facchinetti F. Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials. Gynecological Endocrinology. 2012;28(7):509–15. https://doi.org/10.3109/09513590.2011.650660

[16] Lesoine B, Regidor P-A. Prospective randomized study on the influence of myoinositol in PCOS women undergoing IVF in the improvement of oocyte quality, fertilization rate, and embryo quality. International Journal of Endocrinology. 2016:4378507. https://doi.org/10.1155/2016/4378507

[17] Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS).Gynecological Endocrinology. 2017;33(1):39–42. https://doi.org/10.1080/09513590.2016.1236078

[18] Luque-Ramírez M, Escobar-Morreale HF. Treatment of polycystic ovary syndrome (PCOS) with metformin ameliorates insulin resistance in parallel with the decrease of serum interleukin-6 concentrations.Hormone and Metabolic Researc. 2010;42(11):815–20. https://doi.org/10.1055/s-0030-1262855

[19] Yasmin E, Glanville J, Barth J, Balen AH. Effect of dose escalation of metformin on clinical features, insulin sensitivity and androgen profile in polycystic ovary syndrome. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2011;156(1):67–71. https://doi.org/10.1016/j.ejogrb.2010.12.041

[20] Fux Otta C, Wior M, Iraci GS, Kaplan R, Torres D, Gaido MI, et al. Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. Gynecological Endocrinology. 2010;26(3):173–8. https://doi.org/10.3109/09513590903215581

[21] Victor VM, Rovira-Llopis S, Bañuls C, Diaz-Morales N, Lopez-Domenech S, Escribano-López I, et al. Metformin modulates human leukocyte/endothelial cell interactions and proinflammatory cytokines in polycystic ovary syndrome patients. Atherosclerosis. 2015;242(1):167–73. https://doi.org/10.1016/j.atherosclerosis.2015.07.017

[22] Özay AC, Emekçi Özay Ö, Okyay RE, Gülekli B. The effect of myoinositol on ovarian blood flows in women with polycystic ovary syndrome. Gynecological Endocrinology. 2019;35(3):237–41. https://doi.org/10.1080/09513590.2018.1520827

[23] Tagliaferri V, Romualdi D, Immediata V, De Cicco S, Di Florio C, Lanzone A, et al. Metformin vs myoinositol: which is better in obese polycystic ovary syndrome patients? A randomized controlled crossover study. Clinical Endocrinology. 2017;86(5):725–30. https://doi.org/10.1111/cen.13304

[24] Soldat-Stanković V, Popović-Pejičić S, Stanković S, Prtina A, Malešević G, Bjekić-Macut J, et al. The effect of metformin and myoinositol on metabolic outcomes in women with polycystic ovary syndrome: role of body mass and adiponectin in a randomized controlled trial. Journal of Endocrinological Investigation. 2022;45(3):583–95. https://doi.org/10.1007/s40618-021-01691-5

[25] Shokrpour M, Foroozanfard F, Afshar Ebrahimi F, Vahedpoor Z, Aghadavod E, Ghaderi A, et al. Comparison of myo-inositol and metformin on glycemic control, lipid profiles, and gene expression related to insulin and lipid metabolism in women with polycystic ovary syndrome: a randomized controlled clinical trial. Gynecological Endocrinology. 2019;35(5):406–11. https://doi.org/10.1080/09513590.2018.1540570

[26] Kazerooni T, Dehghan-Kooshkghazi M. Effects of metformin therapy on hyperandrogenism in women with polycystic ovarian syndrome. Gynecological Endocrinology. 2003;17(1):51–6. https://doi.org/10.1080/713603186

[27] Kurzthaler D, Hadziomerovic-Pekic D, Wildt L, Seeber BE. Metformin induces a prompt decrease in LH-stimulated testosterone response in women with PCOS independent of its insulin-sensitizing effects. 2014;12(1):98. https://doi.org/10.1186/1477-7827-12-98

[28] Xue L, Chen F, Yue F, Camacho L, Kothapalli S, Wei G, et al. Metformin and an insulin/IGF-1 receptor inhibitor are synergistic in blocking growth of triple-negative breast cancer. Breast Cancer Research and Treatment. 2021;185(1):73–84. https://doi.org/10.1007/s10549-020-05927-5

[29] De Leo V, La Marca A, Orvieto R, Morgante G. Effect of metformin on insulin-like growth factor (IGF) I and IGF-binding protein I in polycystic ovary syndrome. The Journal of Clinical Endocrinology and Metabolism. 2000;85(4):1598–600. https://doi.org/10.1210/jcem.85.4.6560

[30] Sharma S, Mathur DK, Paliwal V, Bhargava P. Efficacy of metformin in the treatment of acne in women with polycystic ovarian syndrome: A newer approach to acne therapy. The Journal of Clinical and Aesthetic Dermatology. 2019;12(5):34–8. https://pubmed.ncbi.nlm.nih.gov/31320975/
[31] Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertility and Sterility. 2000;73(6):1149–54. https://doi.org/10.1016/s0015-0282(00)00501-x
[32] Merviel P, James P, Bouée S, Le Guillou M, Rince C, Nachtergaele C, et al. Impact of myo-inositol treatment in women with polycystic ovary syndrome in assisted reproductive technologies. Reproductive Health. 2021; 18(1):13. https://doi.org/10.1186/s12978-021-01073-3
[33] Ciotta L, Stracquadanio M, Pagano I, Carbonaro A, Palumbo M, Gulino F. Effects of myo-inositol supplementation on oocyte's quality in PCOS patients: a double blind trial. European Review for Medical and Pharmacological Sciences. 2011;15(5):509–14. https://pubmed.ncbi.nlm.nih.gov/21744744/
[34] Gupta D, Khan S, Islam M, Malik BH, Rutkofsky IH. Myo-inositol's role in assisted reproductive technology: Evidence for improving the quality of oocytes and embryos in patients with polycystic ovary syndrome. Cureus. 2020;12(5):e8079. https://doi.org/10.7759/cureus.8079

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Patricia Acosta, Cenk Mustafa Güven, Jeremy Y. Ng
Article Dates: Received Apr 03 23; Accepted Jul 10 23; Published Sep 04 23

Citation
Please cite this article as follows:
Matossian GA, Buklarewicz IM, Moosa VA. The effects of metformin and myo-inositol on hyperandrogenism, insulin sensitivity, and fertility in polycystic ovary syndrome: A literature review. URNCST Journal. 2023 Sep 04: 7(9). https://urncst.com/index.php/urncst/article/view/483
DOI Link: https://doi.org/10.26685/urncst.483

URNCST Journal
"Research in Earnest"

Funded by the Government of Canada | Canada