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Review Article

Combination of metformin and myoinositol: a powerful weapon to combat polycystic ovary syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) affects up to 13% of women of reproductive age, causing symptoms like menstrual irregularities, insulin resistance, and infertility. Insulin resistance is the root cause of PCOS. Metformin, an insulin-sensitizing drug, and Myo-inositol, a natural compound that enhances ovarian function and also an insulin sensitising agent, have both shown benefits in PCOS management. When combined, these agents act synergistically, that results in improved menstrual cycle regularity, reduction in hyperandrogenic symptoms, and enhancement in fertility outcomes. Recent clinical evidence supports this dual approach, and its approval for PCOS-related infertility treatment in India, along with endorsement by FOGSI, underscores its effectiveness as a promising therapeutic option for women with PCOS.

Keywords: Insulin resistance, Insulin sensitizers in PCOS, Infertility associated with PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) stands as one of the most predominant endocrine system disorder, which affects around 10-13% of women of reproductive age.[1] Studies have indicated that PCOS prevalence is increasing in India, and it stands at 11.34% in the country.[2] Common symptoms include heavy, prolonged, irregular, or absent periods, hyperpigmentation at the neck area, infertility, acne, or oily skin, growth of facial hairs, male-pattern baldness or hair thinning, and weight gain, particularly around the abdomen. Women having PCOS are also at a higher risk of developing comorbidities such as type 2 diabetes, high cholesterol levels, and heart diseases. PCOS can also contribute to anxiety, depression, and negative body image. These symptoms may lead to social stigma, that may impact various aspects of life including family, relationships, work, and social life.[3] Women with PCOS often experience insulin resistance, which affects other hormonal levels and contributes to the complexity of PCOS. Additionally, elevated androgen levels in these women can disrupt ovulation by hindering the release of eggs that results in irregular menstrual cycles.[4]

The insulin receptor is a member of the ligand-activated receptor and tyrosine kinase family of transmembrane signalling proteins and it collectively serves as fundamentally important regulator of cell differentiation, growth, and metabolism.[5] Research shows that in insulin resistance, the signalling pathway from the insulin receptor to the subsequent pathway gets affected. It plays a huge role in PCOS as it affects around 35-80% of women with PCOS. Obesity worsens insulin resistance, though it can also be present in lean individuals.[6] A study has shown that Insulin Resistance is present in 76.9% of Indian women with PCOS.[7] So, it is evident that insulin resistance is the underlying cause of PCOS in women of the Indian phenotype.

Almost 50% of testosterone in the body is bound to sex hormone binding globulin (SHBG).[8] Studies have shown that insulin resistance reduces the levels of SHBG which results in increase in the amount of free testosterone that exacerbates the symptoms of hyperandrogenism.[9]

Insulin resistance results in hyperinsulinemia and results in increase in the LH: FSH ratio, and that leads to decreased FSH levels.[10] Anti-Mullerian hormone (AMH) has been identified as a key factor influencing the LH: FSH ratio. It correlates positively with hyperandrogenism and insulin resistance. Increased AMH levels are associated with increased LH and decreased FSH. These factors cumulatively are responsible for the cyst formation in the ovary which is the hallmark symptom of PCOS.[11] Insulin resistance also adversely affects oocyte quality and embryo implantation. Insulin resistance can lead to oxidative stress and impaired energy metabolism, and it results in an an unfavourable environment for the oocyte development at the ovary. The reduced expression of glucose transporters like glucose transporter type 4 (GLUT-4) in endometrial tissues can lead to glucose deficiency which can adversely affect the process of implantation.[12]

The current clinical management of PCOS primarily focuses on offering symptomatic relief. Various interventions focus on achieving therapeutic goals such as regulating the menstrual cycle, treating hyperandrogenism, managing body weight, increasing insulin sensitivity, improving metabolic disturbances, concomitantly by promoting lifestyle changes. Medications such as metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, and thiazolidinediones are commonly prescribed for individuals with PCOS when insulin resistance is identified as the root cause.[13] Research is continually evolving to achieve optimal treatment outcomes for patients with PCOS. Recently, the combination of metformin and myo-inositol has emerged as a promising approach in improving the metabolic and reproductive parameters in women with PCOS. The aim of this review is to evaluate the clinical evidence supporting the use of a combination of metformin and myo-inositol in the management of PCOS and to determine whether this combination therapy provides superior outcomes compared to monotherapy with either agent.

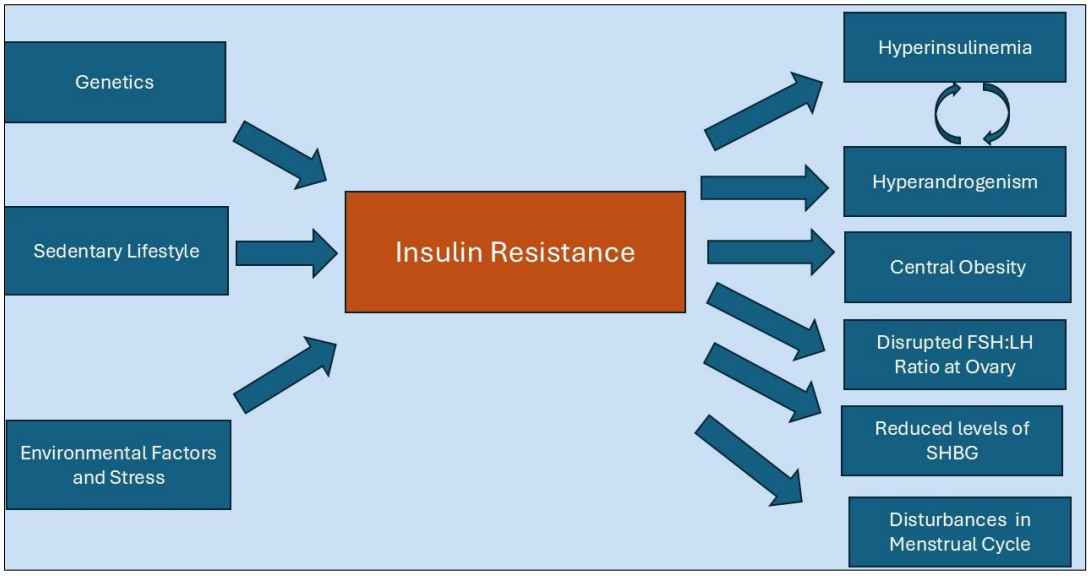

Figure 1: Insulin resistance: the root cause of PCOS.

DISCUSSION

Role of metformin in PCOS

Metformin has been in use as an antidiabetic drug since a long time. It is inexpensive and a safe drug. The international guidelines for management of PCOS recommend metformin for managing PCOS, especially in adults with a BMI of 25 kg/m² or higher. Metformin corrects metabolic disturbances like insulin resistance, glucose levels, and lipid profiles. Metformin may also be considered in adults with low BMI.[1] There are several studies that recommend metformin in obese women with PCOS as it promotes weight loss, improves metabolic conditions, regulates menstrual cycles, restores ovulation, and increases the rate of conception.[14] Research has shown that metformin increases insulin sensitivity by enhancing the activity of phosphatidylinositol 3-kinase (PI3K) and 5' adenosine monophosphate-activated protein kinase (AMPK) at the insulin receptors. The activation of PI3K and AMPK leads to promotion of glucose uptake at the peripheral muscle tissues.[15,16] A Cochrane review suggested that Metformin is beneficial for women with anovulatory fertility.[17] El Maghraby et al conducted a study involving 117 adolescent girls with PCOS, who were randomized into three groups: group A received 1700 mg/day of metformin, group B received a combined oral contraceptive pill (30 µg ethinyl estradiol and 15 mg progestin/day), and group C served as the control group

with no treatment. The results showed a significant reduction in fasting and after-load insulin levels, with metformin being associated with considerable weight loss. These findings indicated that metformin significantly improves metabolic parameters in adolescent girls with PCOS.[18] A recently published study was carried to compare effectiveness of monotherapy of metformin and myo-inositol. 80 women with PCOS were divided into two groups. One group was treated with 1500 mg/day of metformin in three divided doses, and the other group received 1000 mg/day of Myo-inositol for 12 weeks. Both treatments led to notable improvements in parameters such as BMI, blood glucose, and insulin levels. However, metformin was observed to yield higher HDL levels and slightly better conception rates (40% compared to 25%) than myo-inositol. Metformin was found to have superior effectiveness in enhancing fertility and raising HDL levels.[19] Guan et al analyzed data from 12 randomized controlled trials involving 683 participants. The study focused on women with a BMI greater than 25 kg/m² who received metformin as the primary intervention. It was concluded that that metformin significantly reduced BMI, waist circumference, and improved various endocrine and metabolic indicators in obese women with PCOS.[20] Abdalla et al reviewed 24 randomized controlled trials involving 564 women with PCOS who were treated with metformin. Their analysis revealed significant reductions in LDL cholesterol, BMI, body weight, fasting blood glucose and total testosterone. An increased clinical pregnancy rate was also noted following metformin intervention. These outcomes emphasize the favourable impact of metformin therapy for women with PCOS.[21]

Role of myo-inositol in PCOS

Myo-inositol is a naturally occurring carbohydrate, specifically a stereoisomer of inositol, which is a six-carbon cyclic compound with six hydroxyl groups. It was once regarded as a B vitamin (vitamin B8); however, it is not classified as an essential nutrient since it is synthesized from glucose in the body. Myo-inositol is essential for mediating the granulosa cells' response to FSH stimulation in the ovary. This is important for the development and function of ovarian follicles. After entering the cells, myo-inositol is converted into phosphatidyl-myo-inositol, and it subsequently transforms into inositol-triphosphate, it then acts as an intracellular secondary messenger for insulin at the peripheral tissues and follicular stimulating hormone at the ovary. This process of oocyte maturation is essential for the enhanced fertility outcome especially in women with PCOS with anovulatory infertility.[22,23] Inositols are considered as safe and may offer metabolic improvements and clinical benefits.[1] High Myo-inositol levels are associated with better oocyte quality at the ovary.[24]

The 2023 evidence-based guidelines on PCOS suggest that inositol in any form may be considered for women with PCOS, based on personal preferences and values.[1] Clinical evidence supports the safety and efficacy of myo-inositol in managing PCOS. Various studies have shown the effectiveness of myo-inositol in improving insulin resistance and ovarian function. Zeng et al examined data from 10 trials with 573 infertile women with PCOS. Homeostasis model assessment of insulin resistance (HOMA-IR) index and estrogen levels improved significantly with myo-inositol.[25] Regidor et al investigated 3602 infertile women with PCOS who received 4000 mg of myo-inositol daily along with folic acid for 2-3 months. Ovulation was restored in 70% of the participants. Interestingly, there was an improvement in the pregnancy rate which was improved by 15.1% with the intervention. There was a significant decrease in the testosterone levels from 96.6 ng/ml to 43.3 ng/ml. The study concluded that myo-inositol can enhance outcomes in women experiencing infertility linked to PCOS.[26] Raffone et al compared metformin and myo-inositol in 120 women with PCOS over six months. While both groups showed improvements, the myo-inositol group achieved better outcomes in restoring spontaneous ovulation (65% versus 50%) and pregnancy rates (30% versus 18.3%). The study underlined myo-inositol's greater effectiveness in promoting ovulation and conception compared to metformin.[27] Collectively, these studies suggest that myo-inositol is a safe and effective option for managing PCOS-related infertility and metabolic symptoms.

Rationale and effectiveness of combination of metformin and myo-inositol in women with PCOS

The combination of metformin and myo-inositol may provide a promising treatment for PCOS. They both synergistically target the common underlying problems of insulin resistance, hyperandrogenism, and menstrual irregularities. As previously discussed, metformin is an insulin-sensitizing agent that reduces insulin levels, which in turn helps correct other hormonal imbalances associated with PCOS. Myo-inositol is a naturally occurring substance in the vitamin B family which further improves insulin sensitivity while providing other advantageous effects both on ovarian function and has been shown to increase ovulatory function and the regularity of menstrual cycles. Metformin and myo-inositol work through different mechanisms in improving the insulin sensitivity. Drug Controller General of India has also approved the combination for the management of infertility associated with PCOS.[28] The Federation of Obstetric and Gynaecological Societies of India (FOGSI) has recently endorsed the combination of metformin and myo-inositol as a first line therapy for the management of infertility associated with PCOS.[29]

Many clinical studies have highlighted the benefits of combining metformin and myo-inositol for improved outcomes in the treatment of PCOS. Kriplani et al compared a fixed-dose combination of metformin (500 mg SR) and myo-inositol (600 mg) to metformin monotherapy in 173 Indian women with PCOS for over 24 weeks. The results of the study demonstrated that, met-myo combination therapy had major advantages over metformin monotherapy in improving metabolic and reproductive parameters in women with PCOS. At 24 weeks, 75% of patients in the met-myo group achieved

significant improvement in HOMA-IR compared to 60.67% in the met group. Normal menstrual frequency was restored in 88.1% of patients of combination therapy versus 75.28% in the met group. 90.48% of patients in the met-myo group had normal menstrual blood flow (5–80 ml) compared to 76.40% in the met group. Both groups exhibited significant reductions in serum testosterone levels and increase in serum estradiol levels. Additionally, BMI decreased significantly in both the groups, with a more prominent reduction observed in the met-myo group. The combination therapy was well-tolerated, and there were no treatment discontinuations due to side effects in either group.[30] Samatha et al conducted a large-scale study of 710 women with PCOS over 6 and 12 months. Combination therapy showed the greatest improvements in menstrual symptoms, fasting insulin levels, and BMI compared to monotherapy with either agent. This study demonstrates that the combined treatment consistently improves both metabolic and reproductive health in women with PCOS.[31] Zainab et al studied 54 women with PCOS. The effects of metformin, myo-inositol, and their combination was evaluated on hormonal parameters in the PCOS women. The combination therapy group demonstrated the most pronounced reductions in testosterone levels, an improved LH/FSH ratio, and significant reduction in serum testosterone levels.[32] Rani et al evaluated 48 infertile women with PCOS over 12 weeks. Women receiving a combination of metformin (500 mg thrice daily) and myo-inositol (1000 mg twice daily) had significantly higher ovulation and pregnancy rates compared to those receiving metformin alone. The combination group also showed higher serum progesterone levels and a greater number of mature follicles.[33] Agrawal et al conducted a study on 120 infertile women with PCOS and assessed the efficacy of a combination of metformin (500 mg) and myo-inositol (600 mg) thrice daily. The combination therapy group showed improvements in menstrual cycle regularity, improvement in HOMA-IR levels, and significantly higher live birth rates compared to metformin alone therapy.[34]

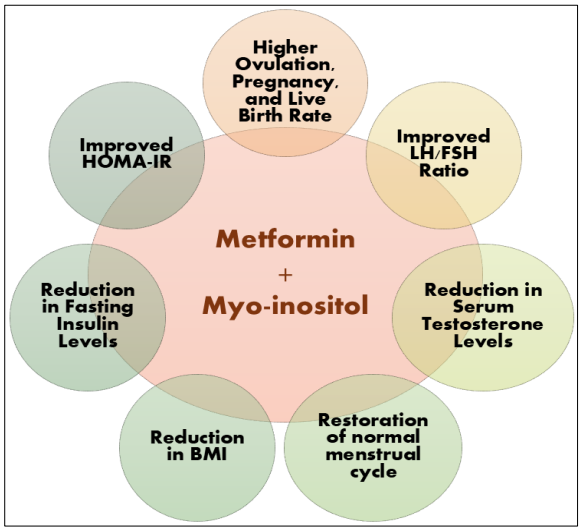

Figure 2: Synergistic benefits of metformin and myo-inositol in PCOS management.

CONCLUSION

The combination of metformin and myo-inositol seems to be a promising approach to managing problems associated with PCOS. This synergistic duo can help alleviate common PCOS symptoms like irregular menstruation, hyperandrogenism and infertility. It addresses the underlying root cause of insulin resistance. The recent endorsement by the DCGI and FOGSI for using this combination in treating PCOS related infertility further supports the clinical potential of the combination. So, for women with PCOS, particularly those struggling with insulin resistance and associated metabolic challenges, the metformin and myo-inositol combination offers a safe, effective, and well-tolerated option that supports long-term health and reproductive success.

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