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Review Article

Metformin and myoinositol for polycystic ovary syndrome: A review of their combined effectiveness

Ameet Patki[1], Kaberi Banerjee[2], Basab Mukherjee[3], Sushrut Oza[4]*

[1]Dept. of Obstetrics and Gynecology, Fertility Associates, Mumbai, Maharashtra, India
[2]Dept. of Obstetrics and Gynecology, Advance Fertility and Gynaecology Centre, New Delhi, India
[3]Dept. of Obstetrics and Gynecology, Medical College and Hospital, Kolkata, West Bengal, India
[4]Dept. of Medical Affairs, Eris Lifesciences, Ahmedabad, Gujarat, India

Abstract

Polycystic ovary syndrome (PCOS) is a prevalent endocrine heterogeneous disorder. The complex etiology of PCOS involves hormonal imbalances, genetics, lifestyle, and environmental factors. Insulin resistance is one of the most significant pathophysiological traits in both obese and lean females with PCOS. Both obese and lean women with PCOS are vulnerable to the problem of insulin resistance. The Indian phenotype has been shown to have a predominance of PCOS associated with insulin resistance. Insulin sensitizers improve insulin sensitivity, thereby lowering insulin levels and managing the hormonal and metabolic abnormalities associated with PCOS. Insulin sensitizers like metformin, inositols, and chromium are commonly used in the treatment of PCOS. Metformin and Myoinositol in combination have been found to be synergistically beneficial for alleviating the symptoms of PCOS by enhancing insulin sensitivity at the different targets in the cascade of insulin resistance. Recent data from clinical trials and meta-analysis has highlighted the potential benefits of combining metformin and myoinositol in managing PCOS symptoms such as menstrual irregularity, hyperandrogenism, insulin resistance, and infertility. The aim of this review is to summarize currently available data on the metformin and myoinositol combination therapy in PCOS patients.

Keywords: Polycystic ovary syndrome, Insulin resistance, Metformin, Myoinositol.

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1. Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy that affects reproductive-aged women, with impacts across the lifespan from adolescence to post-menopause.[1] The worldwide prevalence of PCOS currently stands at 10-13%.[1] The prevalence of PCOS is continuously rising in India, and it ranges between 3.7-22.5% in the reproductive age group.[2] The estimated prevalence of PCOS in adolescents is around 9.13% to 20%.[3,4] Symptoms of PCOS can vary from person to person and may fluctuate over time without a clear trigger. The reproductive complications of PCOS include irregular, or absent periods, infertility, excessive facial or body hair, male-pattern baldness, acanthosis nigricans. Insulin resistance has been found to be a classical feature in the Indian phenotype of women with PCOS.[5] Individuals with PCOS are also at a higher risk of developing metabolic syndromes that includes diabetes mellitus, hypertension, dyslipidemia, cardiovascular diseases. With rising rates of PCOS, particularly in India, and its strong association with insulin resistance and metabolic complications, this review aims to evaluate the therapeutic potential of Metformin and Myoinositol combination for the effective management of PCOS. With rising rates of PCOS, particularly in India, and its strong association with insulin resistance and metabolic complications, this review aims to evaluate the therapeutic potential of Metformin and

*Corresponding author: Sushrut Oza
Email: sushrutoza@gmail.com

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Myoinositol combination for the effective management of PCOS.

2. Role of Insulin Resistance in the Pathophysiology of PCOS

Epidemiological data suggests that Insulin Resistance and compensatory hyperinsulinemia are present in 65–95% of women with PCOS, this includes the majority of women who are overweight or obese, along with over half of women who have a normal weight.[6] Women with PCOS have lower insulin sensitivity compared to the control subjects with an average reduction of 27%.[7] A study has shown that Insulin Resistance is present in 76.9% of Indian women with PCOS.[8] A high prevalence of around 35%, Abnormal Glucose Tolerance (AGT) was observed among a large cohort of young Indian women with PCOS as determined by the Oral Glucose Tolerance Test (OGTT).[9] Research shows that women with PCOS are almost twice as likely (incidence rate of 1.95) to develop diabetes compared to the general population. (**Figure 1**) This risk is even higher for those with a higher starting weight or blood sugar levels.[10]

3. Defects in Insulin Signalling Cascade in PCOS

The insulin receptor is a member of the ligand-activated receptor and tyrosine kinase family of transmembrane signalling proteins and it collectively serves as a fundamentally important regulator of cell differentiation, growth, and metabolism.[11] In PCOS patients with insulin resistance, there's a disruption in the normal insulin signalling pathway.[12] Insulin resistance that is related to PCOS often results in reduced activation of PI3 kinase. Research suggests that insulin resistance leads to increased serine phosphorylation of IRS-1, which disassociates IRS-1 from PI3K signalling and results in insulin resistance. It further leads to a reduction in IRS-1 in the skeletal muscles.[13] It results in reduced efficiency to promote glucose uptake into the peripheral tissues. It is then followed by, GLUT4 transporters not moving to the cell surface as effectively. This reduces glucose uptake into cells, even though increased levels of insulin. The combined effect of reduced PI3 kinase activity and impaired GLUT4 translocation is decreased glucose uptake by cells. This contributes to PCOS symptoms like hyperinsulinemia, hyperglycemia due to reduced glucose uptake and metabolic disturbances like weight gain, lipid abnormalities, and other PCOS related complications.[14] (**Figure 2**)

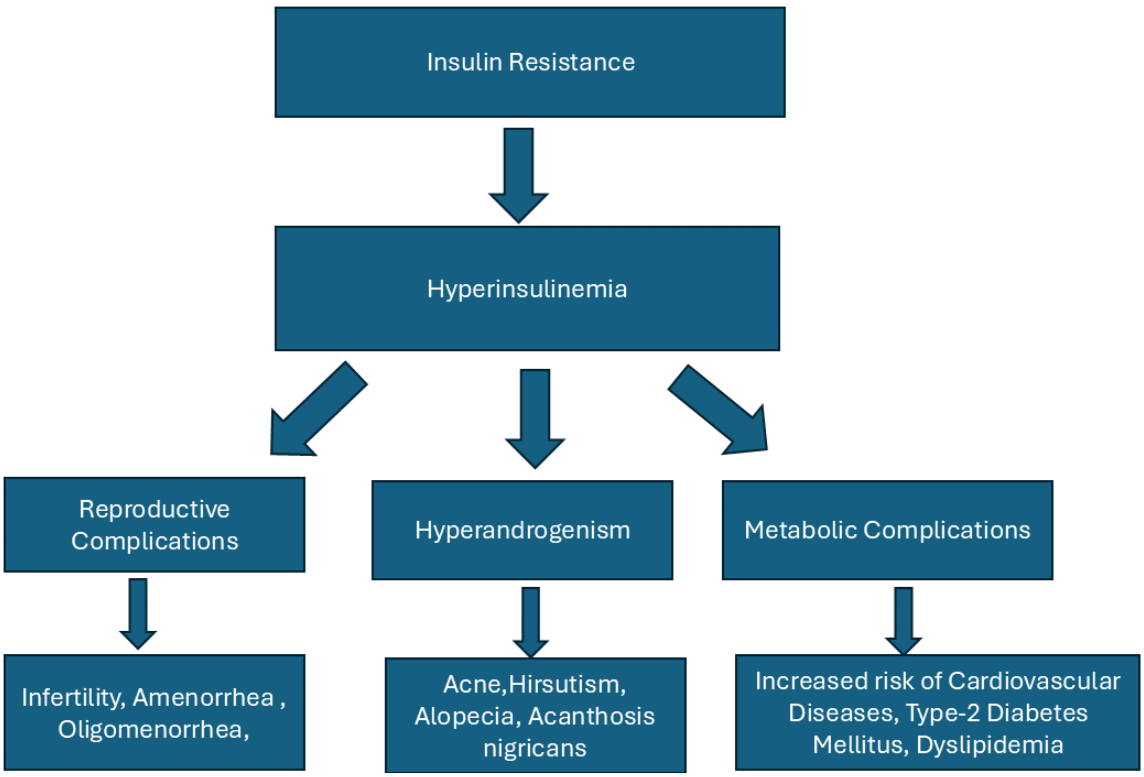
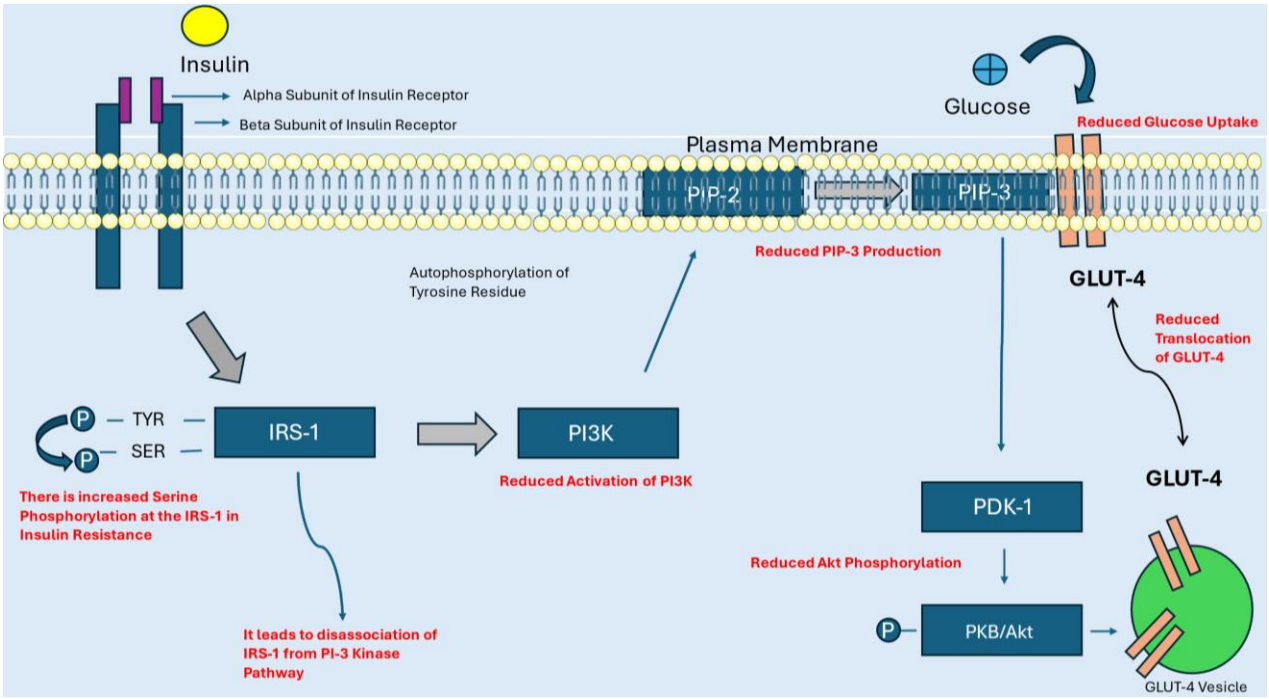


Figure 1: Role of insulin resistance in the pathophysiology of PCOS



(IRS: Insulin Receptor Substrate, PI3K: Phosphoinositide 3-Kinase, PIP: Phosphatidylinositol Biphosphate, PDK-1: 3-Phosphoinositide-dependent kinase 1, PKB: Protein Kinase B, GLUT: Glucose Transporters)

Figure 2: Defects in insulin signalling cascade in the pathophysiology of PCOS

4. Role of Metformin in PCOS

Metformin is commonly used for the treatment of Type 2 diabetes, and it has also gained prominence in managing insulin resistance associated with PCOS. It has been supported by extensive research which includes published Cochrane reviews, systematic reviews, and meta-analyses.[15,16] Documented clinical trials have been conducted in India and globally.[17] The International Evidence-based Guidelines for the Assessment and Management of Polycystic Ovary Syndrome (2023) endorse metformin for the management of PCOS. As per the guidelines Metformin can be considered for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles as well as in adolescents at risk of or with PCOS for cycle regulation.[1] The primary mechanism of action of metformin involves reducing hepatic glucose production and improving peripheral insulin sensitivity. As a result, there is a reduction in blood glucose levels followed by a reduction in insulin levels, which can aid in normalizing hormonal imbalances linked to PCOS.[18] The effectiveness of metformin in managing both metabolic and reproductive symptoms of PCOS makes it an important component of the treatment plan. The adverse effects of metformin are generally modest, such as nausea, constipation, and diarrhea, and are well tolerated. The diabetes prevention program outcome study reported an adherence rate of metformin therapy of over 71%.[19]

4.1. Role of metformin in improving insulin sensitivity cascade

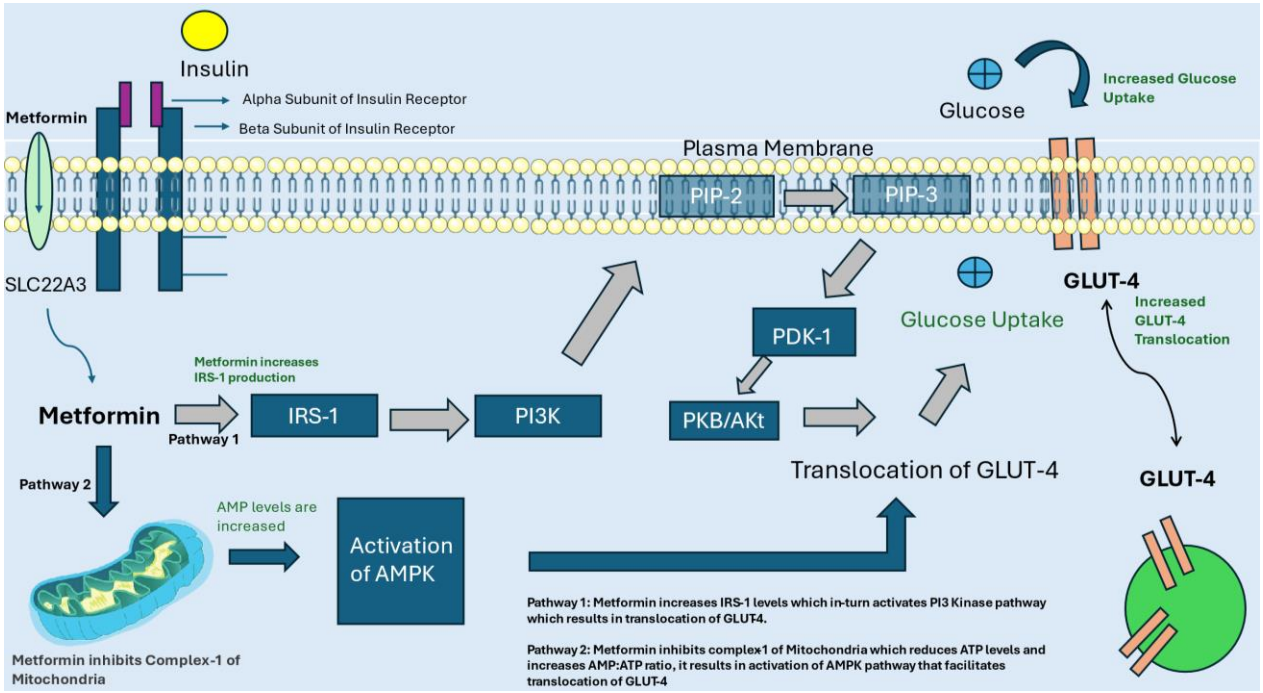
4.1.1. Pathway-1

Metformin also increases the IRS necessary for the activation of PI-3 Kinase.[20] A study has shown that metformin administration resulted in decreased levels of reactive oxygen species and decreased autophagy through modulation of the PI3K/AKT signalling pathway.[21] Additionally, Metformin enhances the insulin-stimulated translocation of GLUT-4 transporters from the cytosol to the membrane in the granulosa cells of the ovary.

4.1.2. Pathway-2

Metformin is also known to directly inhibit Complex I of mitochondria which disrupts mitochondrial respiration and ATP production, thereby inducing cellular energy depletion and a subsequent increase in the AMP: ATP ratio.[22] AMPK (5' adenosine monophosphate-activated protein kinase) regulates cellular and lipid metabolism. AMPK activation increases glucose uptake in skeletal muscle by stimulating GLUT-4 translocation to the cell membrane and thus improves insulin sensitivity.[23]

Metformin is also known to improve endometrial receptivity through various mechanisms. It upregulates GLUT4 expression in the endometrium of PCOS patients, it also significantly increases endometrial vascularity, endometrial thickness, and endometrial volume. Due to its metabolic, endocrine, vascular, and anti-inflammatory effects, metformin enhances markers of endometrial receptivity.[24] (**Figure 3**)



(AMPK: 5' Adenosine Monophosphate-activated Protein Kinase, IRS: Insulin Receptor Substrate, PI3K: Phosphoinositide 3-Kinase, PIP: Phosphatidylinositol Biphosphate, PDK-1: 3-Phosphoinositide-dependent kinase 1, PKB: Protein Kinase B, GLUT: Glucose Transporters)

Figure 3: Mechanism of action of metformin in insulin resistance associated with PCOS

5. Role of Myoinositol in PCOS

Myoinositol is frequently used as an Insulin Sensitizer in the treatment of PCOS. Myoinositol supplementation is known to inhibit glucose absorption and increase glucose uptake into the muscle.[25] PCOS has been linked with deficiency of myoinositol.[26] Myoinositol has been proven to alleviate the reproductive and metabolic abnormalities that are characteristic of PCOS. A meta-analysis of 9 randomized controlled trials has shown that Myoinositol supplementation is effective in improving fasting insulin, HOMA-IR, and testosterone levels.[27] Additionally Myoinositol has also shown significant changes in T, adiponectin, gonadotropins, BMI, and menstrual regularity. It is a widely recognized nutraceutical that enhances the FSH signalling in PCOS patients and also improves ovarian function.[26] Higher concentration of myoinositol is considered to be a marker of good oocyte quality.[28] Myoinositol also has a role in improving the quality of embryos in women with PCOS who undergo various assisted reproductive technology procedures.[29] Myoinositol is considered a safe and well-tolerated treatment option with no significant side effects reported in the clinical studies.

5.1. Role of myoinositol in improving insulin sensitivity cascade

5.1.1. Pathway 1

Myoinositol is transported into cells via coupled proton or sodium transport proteins. The predominant human transporter for Myoinositol is sodium/myoinositol transporter 1 (SMIT-1).[30] Myoinositol has been shown to improve the PI3K signalling pathway, which is important for insulin action. This PI3K signalling pathway regulates various downstream effects, including glycogen synthesis and glucose uptake. Myoinositol is integrated into eukaryotic cell membranes as phosphatidyl-myo-inositol, and its inositol ring can be phosphorylated in seven different ways by kinases, resulting in phosphoinositides like PIP1, PIP2, and PIP3 which play a pivotal role in the process of translocation of GLUT-4 channels and thus assist in the process of glucose uptake.[31] Myoinositol supplementation has also led to increased phosphorylation of Akt and its downstream targets, which enhances insulin sensitivity and glucose metabolism.[32]

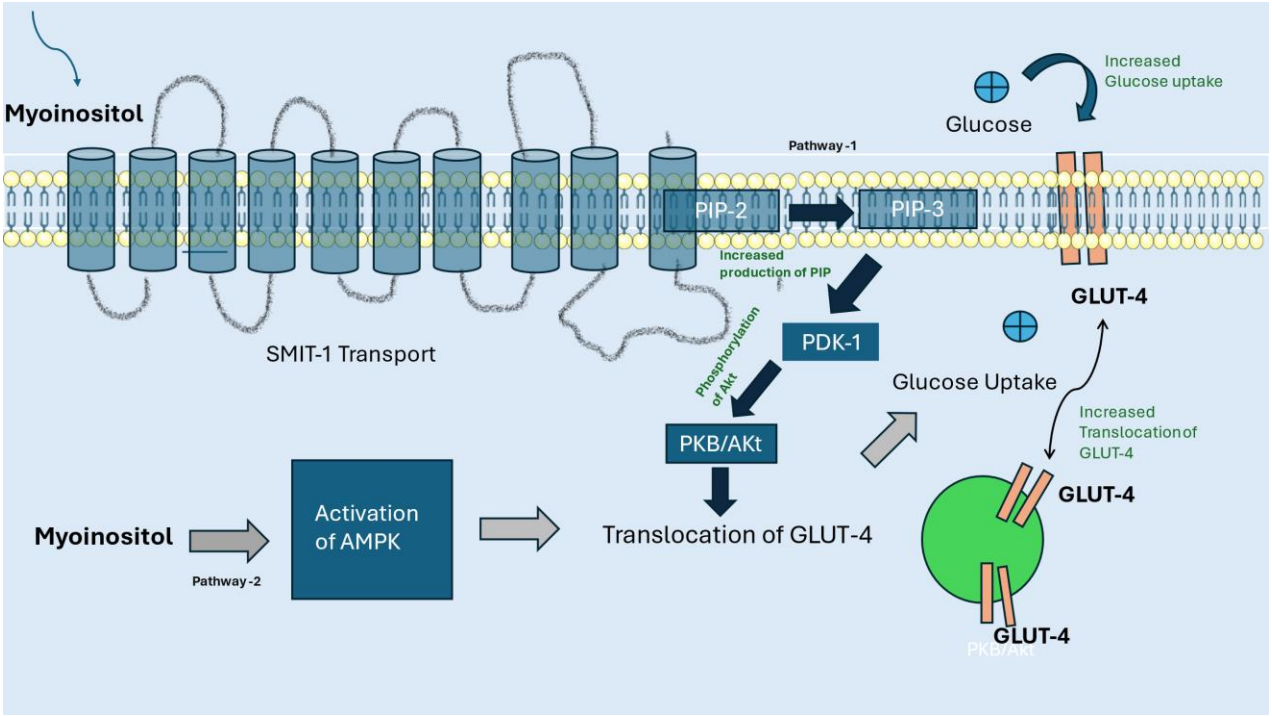
5.1.2. Pathway 2

Research has shown that myoinositol in human endometrial stromal cell lines under hyperandrogenic conditions has shown that it has a role in AMPK activation and expression of GLUT-4.[30] (**Figure 4**)

6. Combination of Metformin and Myoinositol

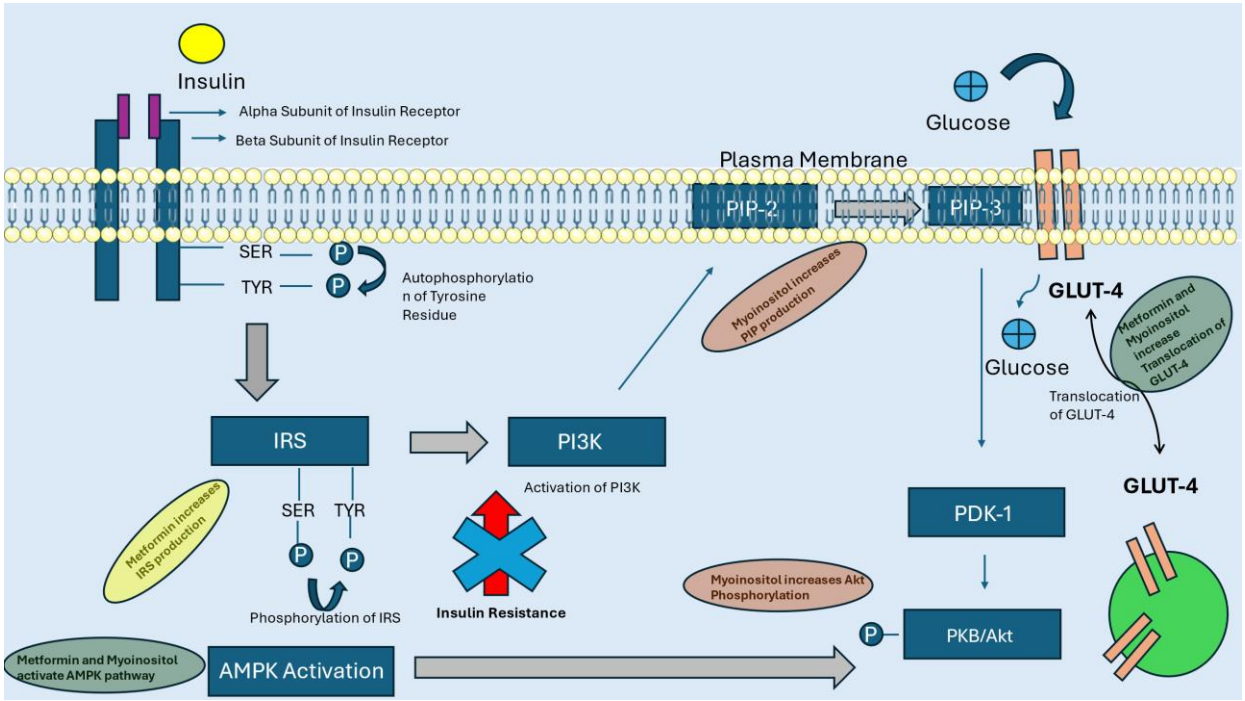
Metformin and Myoinositol are a combination of two different insulin-sensitising agents that acts with multiple mechanisms for improving the clinical status of Insulin Resistance in women with PCOS. (**Figure 5**)

Metformin and myoinositol play vital roles in supporting ovarian and uterine functions in women. Together, Myoinositol and Metformin can enhance the "seed" and the "soil," respectively facilitating the successful implantation. (**Figure 6**)



(AMPK: 5' Adenosine Monophosphate-activated Protein Kinase, PIP: Phosphatidylinositol Biphosphate, PDK-1: 3-Phosphoinositide-dependent kinase 1, PKB: Protein Kinase B, GLUT-4: Glucose Transporters)

Figure 4: Mechanism of action of myoinositol in insulin resistance associated with PCOS



(AMPK: 5' Adenosine Monophosphate-activated Protein Kinase, IRS: Insulin Receptor Substrate, PI3K: Phosphoinositide 3-Kinase, PIP: Phosphatidylinositol Biphosphate, PDK-1: 3-Phosphoinositide-dependent kinase 1, PKB: Protein Kinase B, GLUT: Glucose Transporters)

Figure 5: Mechanism of action of metformin and myoinositol for improving insulin sensitivity in women with PCOS at different sites

Multiple clinical studies have demonstrated that Metformin works synergistically with Myoinositol to improve the overall clinical status of women with PCOS. A recently published meta-analysis with 388 patients has concluded that the Metformin in combination with inositols was associated with menstrual cycle regularization and reduction in hirsutism and LH/FSH ratio compared to metformin monotherapy.[33] The intervention studies are summarized in **Table 1**.

Table 1: Intervention studies with Combination of Metformin and Myoinositol in women affected by PCOS

Author	Subjects and Interventions	Results	Conclusions
Shivani et al.[34]	90 women with PCOS and Vitamin D deficiency divided into 3 groups consisting of 30 women in each group. Group A: 500mg Metformin TID for 24 weeks. Group B: 2000 mg Myoinositol BID for a period of 24 weeks. Group C: 500mg Metformin BID and 2 gm Myoinositol BID for 8 weeks.	a. After treatment, 26%, 50%, and 80% of patients in Groups A, B, and C, respectively, showed regular menstrual cycles. b. After six months, polycystic ovaries were reduced by 50% in Group A, 80% in Group B, and 93.33% in Group C. c. Significant reductions in acne, hirsutism, BMI, serum LH, FSH, LH/FSH ratio, free testosterone, total testosterone, serum insulin, and total cholesterol levels were observed after 24 weeks in all three groups, with the most significant improvements in Group C.	Metformin along with Myoinositol supplementation showed potential therapeutic benefits in improving the hormonal balance and several PCOS related symptoms like menstrual regularity, ovulation and features of hyperandrogenism.
Agrawal et al.[35]	A total of 120 infertile women with PCOS were randomized into two groups: Group I (n = 60) received 500 mg Metformin and 600 mg Myoinositol TID, and Group II received 500 mg Metformin TID. They were advised to try for spontaneous conception. If unsuccessful after three months, they received three cycles of ovulation induction and intrauterine insemination.	a. After 3 months, Group I showed significant improvement in menstrual cycles (both cycle length and bleeding days) compared to Group II. b. The improvement in the HOMA-IR index was also significantly higher in Group I. c. Live birth rate was significantly greater in Group I compared to Group II.	Metformin and myoinositol acting synergistically, have more hormonal, clinical, and reproductive benefits as compared to when one drug is given alone.
Ria et al.[36]	N = 100 women with PCOS. Group I (50 women): 500 mg metformin + 2 gm myoinositol in the evening for 3 months. Group II (50 women): 500 mg metformin TID for 3 months.	a. Transvaginal ultrasonography of ‘ovarian size’ post-treatment showed a statistically significant distinction among both groups in terms of normal ovarian size. b. The variance in pregnancy rates among the two groups was statistically highly significant. There was a statistically significant correlation among pregnancy rates in both groups as per transvaginal ultrasound regarding ovarian size in all patients.	The combination of metformin with myoinositol gives better results in PCOS than metformin alone.
Nagaria et al.[37]	70 women with PCOS were included in the study who received a combination of 500mg metformin and 600 mg myoinositol BID for 3 months.	a. Improvement in menstrual symptoms was observed in 90.09% of subjects. b. Spontaneous onset of menses occurred in all the cases presented with amenorrhea, in nearly 90% within 2 months of the start of treatment. c. 50% of patients with infrequent menses had regular cycles after the treatment. In cutaneous symptoms improvement was seen, in acne (66.66%). d. 25% of the patients with infertility conceived during the study period.	Combined metformin and myoinositol therapy demonstrated significant improvements in clinical outcomes for women with PCOS. Additionally, this therapeutic approach resulted into a reduction in the dosage of each individual drug.

Chhabra and Malik[38]	Infertile women with PCOS and high AMH levels were randomized into three groups: Metformin group Metformin + myoinositol group myoinositol group. Primary outcomes included menstrual regularity, follicle count, LH, AMH, hirsutism, and acne, assessed before and after 3 months of treatment.	a. There was a significant fall in serum AMH levels in all three groups. b. The maximum fall was in the group that received only Metformin. c. Metformin and Myoinositol combined therapy resulted in maximum number of regularisations of menstrual cycles in the subjects. d. There was a significant reduction in the hirsutism score and acne in all the groups.	AMH levels decreased with the treatment. Menstrual cycles became regular, and there was a reduction in hyperandrogenism.
Zainab and Manal[39]	54 female patients with PCOS divided into 3 groups, Group 1: 4000 mg myoinositol OD Group 2: 500 mg metformin OD for two weeks and later BD, Group 3: 4g OD Myo inositol + 500 mg Metformin OD for two weeks, then BD all for three months.	a. Testosterone and HOMA-IR levels decreased significantly in groups 1 and 3. b. Group 3 showed marked reductions in LH, LH/FSH ratio, FSI, hirsutism, and acne severity.	Metformin plus Myoinositol along with lifestyle modifications improve clinical, endocrine, and metabolic parameters in women with PCOS.
Rani et al.[40]	48 insulin-resistant infertile women with PCOS were divided into two groups. Group A (n=23) received metformin 500 mg TID and myoinositol 1000 mg BD for 12 weeks, while Group B (n=25) received 500 mg metformin TID for 12 weeks. Both groups were given letrozole for five days starting on cycle days 2-3.	a. Metformin and myoinositol group had significantly more mature follicles than the metformin alone group. b. Mean serum progesterone was also higher in combination group. c. The ovulation and pregnancy rates were significantly higher in the metformin plus myoinositol group compared to the metformin alone group. d. The mean endometrial thickness was greater in the metformin plus myoinositol group, though this difference was not statistically significant.	The combination of metformin and myoinositol significantly enhanced PCOS treatment outcomes. Compared to metformin alone, the combination group experienced improved follicle development, higher progesterone levels, and substantially increased ovulation and pregnancy rates.
Chirania et al.[41]	76 women with PCOS, irregular cycles, infertility, hirsutism, and acne were divided into three groups. Group A: 1000 mg/day myoinositol, Group B: 1000 mg/day metformin, Group C: 1000 mg/day metformin and 1000 mg/day of myoinositol for 4 months.	a. Treatment with metformin and myoinositol resulted in a statistically significant reduction in body weight, fasting insulin levels, and acne.	Myoinositol plays a definitive role in reducing ovarian dysfunction in PCOS. It significantly improves symptoms, promotes weight loss, and alters hormonal parameters. The combination therapy results are comparable to those with myoinositol alone.
Thakur et al.[42]	72 Patients with PCOS were divided into 3 groups, Group A: 500 mg metformin TID, Group B: 1000 mg Myoinositol BD, Group C: Combination of 500 mg metformin and 550 mg myoinositol BD for 24 weeks.	a. After 24 weeks of treatment, all three groups showed significant improvement in menstrual irregularities, skin symptoms, pregnancy rates, LH/FSH ratio, insulin sensitivity, and HOMA-IR. b. The group treated with the combination of metformin and myoinositol had greater improvements compared to those treated with metformin or myoinositol alone.	Metformin and Myoinositol combination resulted in a more significant reduction in insulin resistance and improvement in metabolic and hormonal profile and also the regularization of menstrual cycles and spontaneous conception than metformin and myoinositol alone.

Figure 6 illustrates the synergistic role of Metformin and Myoinositol in enhancing ovarian and uterine functions in women with PCOS.

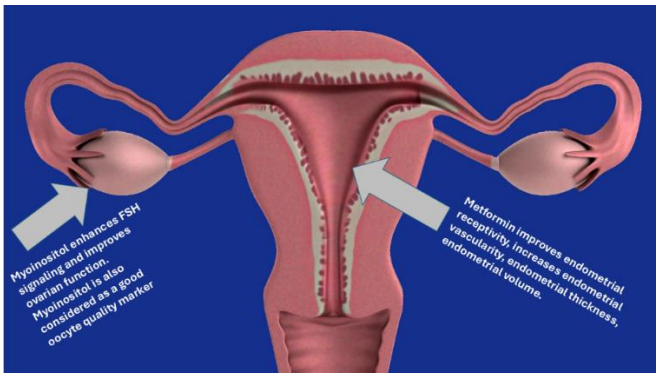


Figure 6: Role of metformin and myoinositol in the ovary and uterus in women with PCOS

7. Conclusion

As per the available literature, the combination of metformin and myoinositol has been shown to significantly alleviate symptoms of PCOS in women. The data suggest that these two agents work synergistically to manage the symptoms of PCOS more effectively than either alone. The combination has the potential to positively influence insulin resistance. Further, metformin and myoinositol have also been shown to improve fertility in women with PCOS and hyperandrogenism. The results discussed in this review lay the groundwork for further research into the management of PCOS. Based on the papers reviewed in this study, the combination seems suitable for managing the root causes of PCOS.

8. Authors' Contributions

Ameet Patki: Conceptualization, Review, and Editing.
Kaberi Banerjee: Literature search and Manuscript review.
Basab Mukherjee: Conceptualization and Manuscript review.
Sushrut Oza: Manuscript writing, Figure and Table preparation.

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None.

10. Conflict of interest

None.

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