



"Metformin for PCOS: A Review of Current Guidelines and Clinical Practice"

J. Vanitha¹, I. Thara², M. Sai Kumar³, Dr. K.T. Naik⁴

^{1,2,3} Pharm. D Interns, Krishna Teja Pharmacy College, Tirupati, Andhra Pradesh.

⁴ Associate professor, Krishna Teja Pharmacy College, Tirupati, Andhra Pradesh

ABSTRACT:

Polycystic Ovary Syndrome (PCOS) is a common hormonal disorder affecting about 10% of women before menopause. It can lead to issues with metabolism, fertility, and mental well-being. Despite its high cost and frequency, many cases go undiagnosed. PCOS is complex and linked to hormone imbalances, insulin resistance, inflammation, and genetic factors. Different diagnostic guidelines exist, with the NIH focusing on hormone levels and ovulation issues, while the Rotterdam criteria also include ovarian appearance. Treatments include birth control pills for menstrual issues and symptoms of excess male hormones, as well as metformin to improve insulin sensitivity. Managing PCOS requires a personalized approach, stressing the need for thorough diagnosis and tailored care.

Key Words: Poly cystic ovarian syndrome, Anovulation, metformin, Insulin Resistance, Obesity, Infertility, Hirsutism, Oral Contraceptives

Abbreviations:

Polycystic ovarian syndrome (PCOS), GnRH (Gonadotropin Releasing Hormone), LH (Luteinizing Hormone), FSH (Follicle Stimulating Hormone), hyperandrogenism (HA), ovulatory dysfunction (OD), polycystic ovarian morphology (PCOM), impaired glucose tolerance (IGT), combined oral contraceptives (COCs), sex hormone-binding globulin (SHBG),

Introduction:

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder distinguished by the manifestation of ovarian cysts, anovulation, and endocrine variation with an estimated 1 in 10 women affected before menopause, many of whom face related complications. (Escobar-Morreale, 2018, Franks, 1995)^[1,2]. Despite causing over USD 8 billion in healthcare costs in the United States, accurate US population-based estimates of incidence and prevalence are lacking and as many as 75% of patients with PCOS are unidentified in clinical practice^[3].

Pathophysiology:

The pathophysiology of this condition is influenced by alterations in steroidogenesis, ovarian folliculogenesis, neuroendocrine function, metabolism, insulin production, insulin sensitivity, adipose cell activity, inflammatory factors, and sympathetic nerve function^[4]

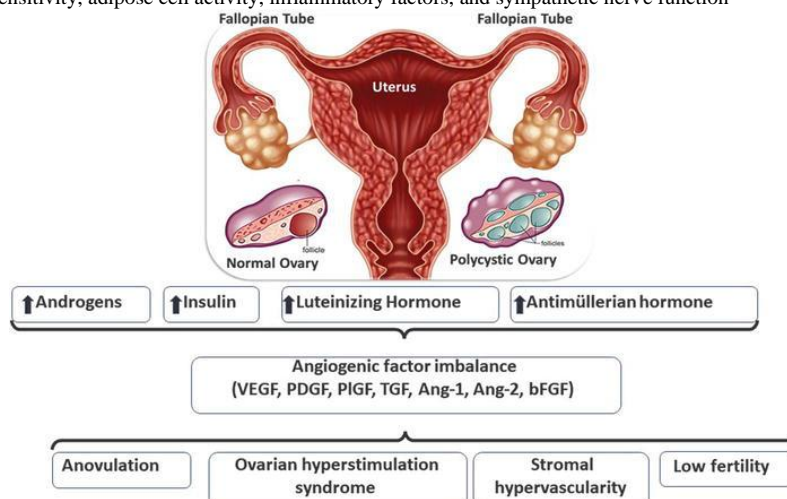


Figure:1 shows the pathophysiology of the PCOS^[5]

Etiology:

The exact cause of PCOS isn't known. Factors that might play a role include:

- **Insulin resistance.** Insulin is a hormone that the pancreas makes. It allows cells to use sugar, your body's primary energy supply. If cells become resistant to the action of insulin, then blood sugar levels can go up. This can cause your body to make more insulin to try to bring down the blood sugar level.

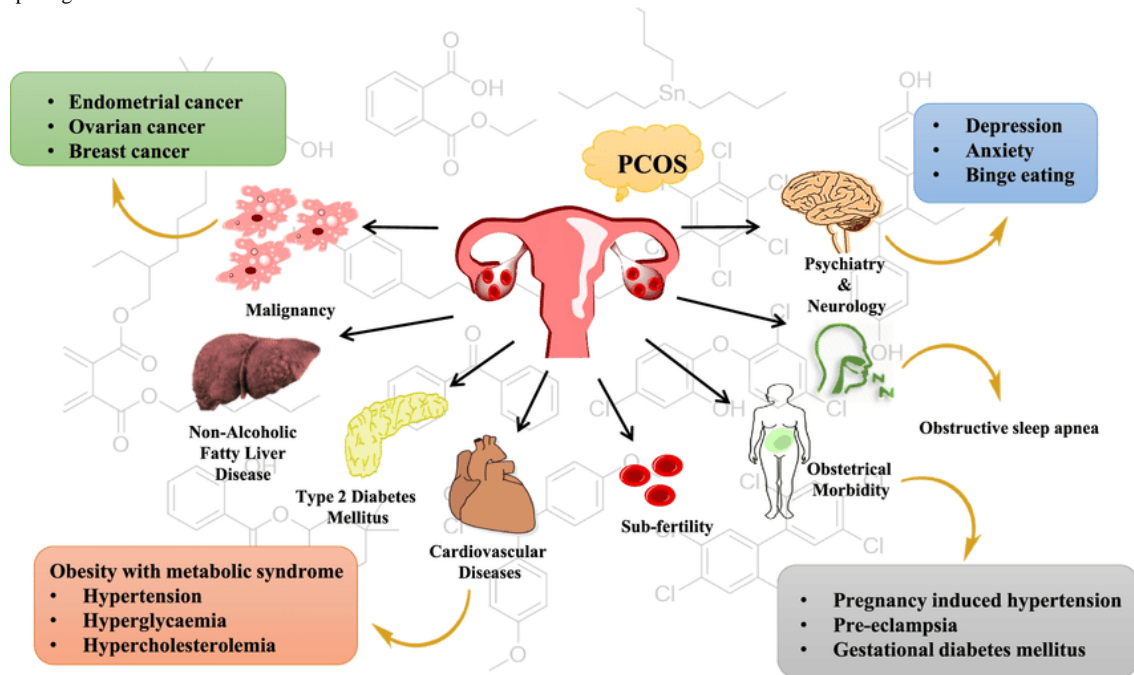
Too much insulin might cause your body to make too much of the male hormone androgen. You could have trouble with ovulation, the process where eggs are released from the ovary.

One sign of insulin resistance is dark, velvety patches of skin on the lower part of the neck, armpits, groin or under the breasts. A bigger appetite and weight gain may be other signs.

- **Low-grade inflammation.** White blood cells make substances in response to infection or injury. This response is called low-grade inflammation. Research shows that people with PCOS have a type of long-term, low-grade inflammation that leads polycystic ovaries to produce androgens. This can lead to heart and blood vessel problems.
- **Heredity.** Research suggests that certain genes might be linked to PCOS. Having a family history of PCOS may play a role in developing the condition.
- **Excess androgen.** With PCOS, the ovaries may produce high levels of androgen. Having too much androgen interferes with ovulation. This means that eggs don't develop on a regular basis and aren't released from the follicles where they develop. Excess androgen also can result in hirsutism and acne^[6]

Risk Factors:

The predisposing risk factors include

**1. Genetics**

2. **Neuroendocrine:** Androgen exposure can also disrupt hormone levels, increasing the frequency of GnRH pulses, which affects the LH:FSH ratio and leads to follicular arrest and abnormal cell development
3. **Lifestyle/Environmental factors:** such as physical activity, lifestyle, diet, and exposure to endocrine-disrupting chemicals and glycotoxins.
4. premature pubarche
5. atypical central precocious puberty
6. obesity syndromes
7. acanthosis nigricans
8. metabolic syndrome^[7]

Risk factors that contribute to the development of Polycystic syndrome as depicted in *Fig:2*^[8]

Symptoms:

Women with PCOS may experience a range of significant health issues, including:

- Psychological symptoms: Reduced quality of life, low self-esteem, depression, and anxiety.
- Reproductive symptoms: Hirsutism, infertility, and complications during pregnancy.
- Metabolic symptoms: Insulin resistance, metabolic syndrome, impaired glucose tolerance (IGT), type 2 diabetes (DM2), and an elevated risk of cardiovascular disease (CVD).

PCOS presents differently throughout life due to its variable nature. Typically, psychological and reproductive symptoms appear in adolescence, while infertility and metabolic complications often increase over time. In cases of obesity, metabolic issues such as IGT, DM2, and metabolic syndrome can emerge as early as adolescence ^[9].

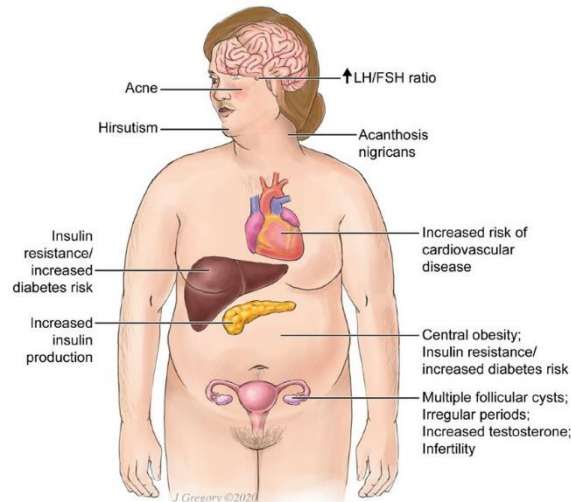


Figure :3 shows the symptoms of the PCOD ^[14]

Diagnosis:

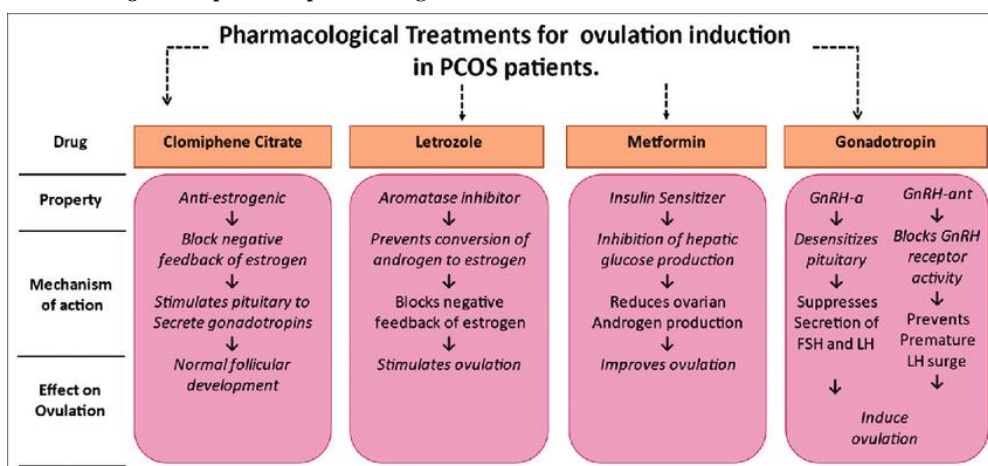
1. **NIH:** The NIH criteria emphasized hyperandrogenism (HA) and ovulatory dysfunction (OD) as primary diagnostic markers, while excluding secondary causes. Notably, polycystic ovarian morphology (PCOM) was excluded since it was observed in 20–30% of women with regular cycles and no signs of hyperandrogenism. Using NIH criteria, the prevalence of PCOS remains 5–8%.
2. **The Rotterdam criteria,** established in 2003 by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine, expanded the diagnostic framework for PCOS. Under these guidelines, a diagnosis requires the presence of any two of the following three features:
 1. **Polycystic Ovarian Morphology (PCOM):** At least twelve small follicles (2-9 mm) in at least one ovary.
 2. **Hyperandrogenism (HA):** Clinical symptoms (e.g., hirsutism, acne) or biochemical evidence of elevated androgens.
 3. **Ovulatory Dysfunction (OD):** Anovulation or oligo-ovulation, often indicated by fewer than nine menstrual periods per year.

The inclusion of PCOM broadened the definition of PCOS beyond the NIH criteria, allowing for a more comprehensive approach to diagnosis ^[11&12].

Management:

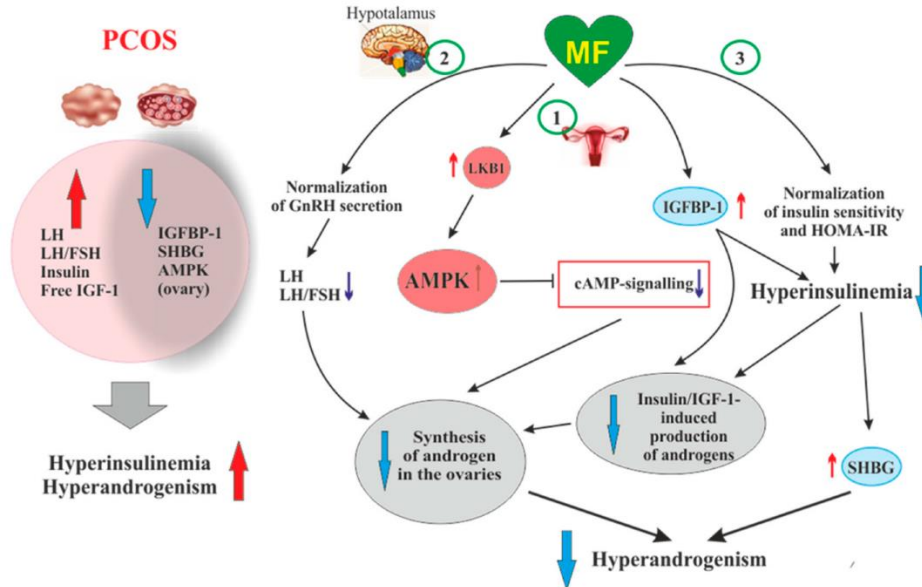
For managing menstrual irregularities and hyperandrogenism in PCOS, combined oral contraceptives (COCs) are the first-choice treatment, with a preference for lower doses of ethinyl oestradiol to minimize side effects. Metformin is mainly recommended for metabolic issues and is more effective than inositol, though it is generally avoided in pregnant women with PCOS. Laser therapy can help reduce hair growth in certain cases, while anti-androgens are reserved for when other treatments are unsuitable or ineffective. For obesity, anti-obesity medications and bariatric surgery may be considered, following general population guidelines for infertility, letrozole is the preferred first-line treatment, with clomiphene plus metformin, gonadotropins, or ovarian surgery as second-line options ^[13].

Figure4: explains the pharmacological treatments for ovulation induction in PCOD ^[14].



Why Is the Role of Metformin In PCOD:

Metformin, a biguanide antihyperglycemic agent, is widely used in PCOS treatment due to its multiple beneficial effects. It helps reduce weight, enhances insulin sensitivity, lowers basal and postprandial glucose, and decreases hepatic glucose production and intestinal glucose absorption. In women with PCOS, metformin has been shown to promote ovulation, improve lipid profiles (lowering LDL and increasing HDL), and alleviate hyperandrogenism and anovulatory infertility, which is often tied to insulin resistance. Although it has significant therapeutic potential, metformin is primarily excreted by the kidneys and is contraindicated in patients with renal impairment^[15]



Metformin's inhibitory effect on hyperandrogenism in PCOS works primarily through two pathways: improving insulin sensitivity and activating the AMPK pathway. By enhancing insulin sensitivity, metformin reduces hyperinsulinemia, which decreases ovarian androgen production and normalizes sex hormone-binding globulin (SHBG) levels, helping to lower circulating androgens.

Metformin also activates the AMPK pathway, which inhibits steroidogenic enzymes in ovarian cells, reducing androstenedione synthesis (a testosterone precursor). This AMPK activation downregulates steroidogenesis and modulates cellular growth. Additionally, metformin supports the LKB1/AMPK pathway, reducing androgen production while promoting estrogen synthesis in granulosa cells, further countering hyperandrogenism in PCOS^[16].

Starting Metformin for PCOS:

Quick route: 500mg a day for 1-2 weeks then, 500mg twice a day for 1-2 weeks then, 500mg three times a day or 850mg twice a day for 1-2 weeks then, 1g (1000mg) twice a day or 850mg three times a day thereafter. Do not increase the dose if side effects develop; move to the slow route below.

Slow route (in women with side effects): Week 1 250mg once a day Week 2 250mg twice a day Week 3 250mg three times a day Week 4 500mg twice a day Week 5 500mg three times a day Week 6 1g twice a day^[17].

Discussion:

Polycystic Ovary Syndrome (PCOS) is a challenging disorder that affects multiple areas of health, including metabolism, reproduction, and mental well-being. The symptoms of PCOS can vary widely, such as high levels of male hormones, irregular ovulation, and metabolic issues, which makes it important to customize diagnosis and treatment for each person. The main diagnostic criteria, like those from NIH and the Rotterdam guidelines, help identify PCOS in a wider range of people, but the different ways PCOS appears can make consistent diagnosis difficult. Current treatments include combined oral contraceptives (COCs) and metformin, which are helpful in managing both hormone imbalances and metabolic issues. Metformin, in particular, is beneficial for improving insulin resistance, lowering androgen levels, and supporting ovulation.

To fully address PCOS, a long-term plan that considers genetic, environmental, and lifestyle factors is needed. Making lifestyle changes, such as improving diet and increasing physical activity, remains an essential part of treatment to manage symptoms and reduce future health risks. More research is necessary to refine diagnostic methods and explore more individualized treatments to better manage the diverse nature of PCOS.

Conclusion :

PCOS is a prevalent but underdiagnosed condition with significant health impacts, including metabolic, reproductive, and psychological challenges. Diagnostic criteria and treatments such as COCs and metformin have improved patient outcomes, though individualized approaches are essential given the disorder's complexity. Continued research into the pathophysiology of PCOS and development of tailored treatment strategies can improve quality of life and long-term health for individuals with PCOS.

REFERENCES:

1. Jeshica Bulsara et al, A review: Brief insight into polycystic ovarian syndrome, *Endocrine and Metabolic Science* Vol 3, 30 June 2021. <https://www.sciencedirect.com/science/article/pii/S266639612100008X>
2. Hosna Mohammad Sadeghi 1: Polycystic Ovary Syndrome: A Comprehensive Review of Pathogenesis, Management, and Drug Repurposing, *Int. J. Mol. Sci.* 2022, 23, 583. <https://pmc.ncbi.nlm.nih.gov/articles/PMC8775814/>
3. Jacob P. Christ et al; Current Guidelines for Diagnosing PCOS, *Diagnostics* 2023, 13, 1113 <https://www.mdpi.com/2195990>
4. Manu et al: Pathophysiology of Polycystic Ovarian Syndrome, 07 January 2022 <https://www.intechopen.com/chapters/79950>
5. Samradhi Singh et al: Polycystic Ovary Syndrome: Etiology, Current Management, and Future Therapeutics, *J. Clin. Med.* 2023.
6. Polycystic ovary syndrome, mayo clinic, Sept. 08, 2022
7. Susan M Sirmans et al: Epidemiology, diagnosis, and management of polycystic ovary syndrome, *Clinical Epidemiology* 2014:6 1–13.
8. Aishwarya Jala et al: ARTICLE Implications of endocrine-disrupting chemicals on polycystic ovarian syndrome: A comprehensive review *Environmental Science and Pollution Research* (2022) 29:58484–58513
9. Dumitrescu R et al: Metformin–Clinical Pharmacology in PCOs, *Journal of Medicine and Life* Vol. 8, Issue 2, April-June 2015, pp.187-192.
10. H Teede, et al: Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan, *BMC Medicine* 2010, 8:41 <http://www.biomedcentral.com/1741-7015/8/41>
11. Sydney Chang et al: Diagnosis of Polycystic Ovary Syndrome: Which Criteria to Use When? *Endocrinol Metab Clin North Am.* 2022 March 01
12. Channa N. Jayasena et al; The management of patients with polycystic ovary syndrome, *Nature Reviews Endocrinology* volume 10, pages624–636 (2014)
13. Helena J. et al; Recommendations From the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome the *Journal of Clinical Endocrinology & Metabolism*, 2023, Vol. 108, No. 10
14. Chouhan P, Garg AK. Ovulation induction in polycystic ovarian syndrome: A review to contemporary approaches. *J Med Soc* 2023; 37:45-50.
15. Howard Craig Zisser, Polycystic Ovary Syndrome and Pregnancy: Is Metformin the Magic Bullet? *Diabetes Spectrum* Volume 20, Number 2, 2007.
16. Alexander et al: Metformin and Polycystic Ovary Syndrome *Encyclopedia.pub*, 23 Aug 2023. <https://encyclopedia.pub/entry/48278#Obstetrics #Gynaecology>
17. Royal Berkshire: Use of Metformin for PCOS, *Centre for Diabetes and Endocrinology* January 2023.