

## A review on Pathophysiology and Treatment of Polycystic Ovary Syndrome

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### ABSTRACT

The most common endocrine disorder in women of reproductive age is PCOS. It has a connection to hirsutism and acne and is a major cause of anovulatory infertility. The usual biochemical characteristics include high blood levels of luteinizing hormone (LH) and testosterone, as well as metabolic problems such insulin resistance and anomalies in energy expenditure. The effect of PCOS on the onset of type 2 diabetes (T2DM) and cardiovascular disease later in life is now well acknowledged. This is because PCOS and obesity are closely related, with obesity increasing PCOS, at least in part. The cause of PCOS is unknown; however it appears to be a complicated illness brought on by a complex interaction between hereditary and environmental variables. There is evidence that the metabolic and endocrine features of PCOS are grouped among families as well. Environmental factors like nutrition and obesity may also influence the phenotypic. Due to PCOS's heterogeneity, there have historically been disputes about its classifications and methods of diagnosis. Restoring fertility, treating metabolic issues, treating androgen excess, and giving endometrial protection are all parts of treatment that must be personalized to the patient's complaints and needs. Due to the intricacy of the condition and its negative effects on quality of life, early detection of complications and effective care of PCOS-related long-term health problems are essential. The ailment, which is currently underdiagnosed, is recognised for women with excruciatingly long delays.

**Keywords:** PCOS, obesity, irregular menstruation, insulin tolerance, genetic polymorphism, TNF alpha gene

### INTRODUCTION

An important social health problem with psychological, metabolic, and reproductive symptoms is polycystic ovarian syndrome (PCOS). Up to 70% of females with PCOS at the age of fertility do not receive a diagnosis, making it the most prevalent endocrine disorder (Teede et al. 2018; Brassard et al. 2016). Females with PCOS might exhibit a variety of symptoms, such as psychological problems including anxiety, sadness, and distorted body views. Additionally, PCOS is linked to reproductive issues such irregular menstruation periods, hirsutism, infertility, and difficulties during pregnancy. In addition, the syndrome is linked to metabolic traits including insulin tolerance, the metabolic disorders, prediabetic condition, type 2 (insulin independent) diabetes mellitus, and several risks linked to cardiovascular factors (Teede et al. 2018). In order to rule PCOS, a patient must have PCOM, ovulatory dysfunction, and hyperandrogenism.

In order to restore fertility, the patient's symptoms and needs should be taken into account while designing a treatment plan that includes triggering ovulation. Altering one's lifestyle, using medications, and maybe undergoing surgery are all treatments aimed at correcting metabolic disorders. When treating hirsutism, alopecia, and/or providing endometrial protection to prevent endometrial cancer are not the main objectives, androgen suppression is required to address these conditions. According to Azziz et al.

2016 and Teede et al. 2018, medical professionals need to focus more on identifying and treating psychological symptoms connected to illness.

### **Diagnostic Features**

The diagnosis of PCOS is still up for debate, according to the Rotterdam ESHRE/ASRM Sponsored PCOS Consensus Workshop Group (2004), because it is difficult to define specific elements within the diagnostic criteria, there is significant clinical heterogeneity that results in a range of phenotypes with or without obesity, there are ethnic differences, and there are variations in clinical features across the life course. As a result, women all around the world report delayed diagnosis, bad diagnostic experiences, and care dissatisfaction. Insufficient research, a lack of thorough worldwide evidence-based recommendations, and a failure to recognise the variety of PCOS's characteristics all contribute to these difficulties (Teede et al. 2018).

The Rotterdam PCOS criteria have been approved by the National Institutes of Health (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004).The majority of medical professionals agree that in order to diagnose PCOS, at least two of the following three conditions must be present: chronic anovulation, clinical or biological hyperandrogenism, and polycystic ovaries (PCOM). Furthermore, it is Crucial to eliminate other conditions that might resemble these PCOS clinical symptoms. These include thyroid disorders,hyperprolactinemia and nonclassical inherited adrenal hyperplasia, (Legro et al. 2013). The Androgen Excess Society, according to Goodman et al. (2015), places less focus on polycystic ovary morphology (PCOM) and more attention on clinical and/or biochemical hyperandrogenism. The Rotterdam criteria should be applied for clinical purposes, according to the latest consensus meeting approved by the NIH.

### **PATHOPHYSIOLOGY**

In the complicated multifactorial disorder known as PCOS, behavioural, endocrine, environmental, and genetic factors are all interconnected. As per Azziz et al. (2016), associated mood disorders, prolongillnesses, and psychosexual dysfunction,the combination of these processes leads to the clinical symptoms of PCOS, like, ovulatory failure, PCOM and hyperandrogenism (Azziz et al. 2016).

### **Hereditary Factors**

It has been established in meta-analyses that genetic polymorphisms in the TNF alpha gene, fibrillin gene, FSHR gene, the FTO gene, androgen receptor, insulin receptor, and certain variants in the IL-6 gene do deliberate a convinced risk for PCOS (Azziz et al. 2016).

### **Endocrine Factors**

The increased LH/FSH ratio results from the pituitary's increased synthesis of LH in conjunction with reduction in release of the follicle-stimulating hormone (FSH) in females with PCOS. The hypothalamic pulse generator for gonadotropin-releasing hormone (GnRH) appears to be main cause of this issue. In young females going through the pubertal transition, this enhanced LH pulsing is already noticeable (Burt Solorzano et al. 2012). Additionally, NK3-R antagonism is presented as a prospective strategy for addressing the central neuroendocrine pathology of PCOS since it particularly lowered the frequency of LH pulses and, therefore, serum LH and testosterone concentrations (George et al. 2016).

### **Extrinsic and Behavioral Contributors**

Regardless of the precise diagnosis, patients with eating disorders (ED) have several traits with women who have PCOS. Both groups are more likely to struggle with depression, anxiety, and body image concerns, all of which can seriously lower quality of life. Due to its independent associations with DM, fatness, and high blood pressure as well as the fact that all of these comorbidities are linked to PCOS, the binge eating disorder (BED) is especially pertinent to this condition (Dokras et al. 2012; Lee et al. 2018). It is noteworthy that women with PCOS frequently say that losing weight is harder for them than for

women without PCOS. As a result, they may be more inclined to practise disordered eating behaviours such as excessive dieting, binge eating, and/or inappropriate compensatory behaviour. Therefore, both the possible influence of ED on the treatment of PCOS and the potential increased risk of ED in individuals with PCOS highlight the need to determine the precise incidence of ED in women with PCOS (Lee et al. 2018). It is certainly crucial to promote weight loss in women with PCOS due to the impact on insulin sensitivity and reproductive function; nevertheless, the potential paradoxical harm of overemphasising the benefits of weight loss cannot be ignored (Lee et al. 2018).

## **TREATMENT**

### **Fertility Dysfunction**

The restoration of normal monoovulation is the ultimate objective of treating PCOS fertility issues. Ovulation induction and ovarian hyperstimulation are two distinct therapy regimens with two distinct therapeutic aims, however many doctors do not differentiate between them. Numerous methods exist to trigger mono-ovulation, including using medications that elevate endogenous FSH levels or giving patients direct FSH injections. In most nations, letrozole can only be taken off-label in situations when anovulatory PCOS women could consider using clomiphene citrate alone to increase ovulation and pregnancy rates. However, women should be made aware that there are other, more potent ovulation inducing medications (Teede et al. 2018).

Gonadotropin therapy may be started if the first-line cure is unsuccessful or if patients show resistance to the oral medicine because they do not ovulate. Again, the goal is to induce one dominant follicle. Gonadotrophin therapy is effective for treating infertility in women with PCOS under the supervision of specialists, with close monitoring using ultrasound and strict criteria to terminate cycles in case of multiple follicle development, according to the Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group (2008). In comparison to the use of oral antiestrogens and/or no medication at all, gonadotropin therapy offers superior per cycle, cumulative pregnancy, and live birth rates (Wang et al. 2017). Although the risk of multiple pregnancies is higher and the expense of medicine is higher when compared to oral medications, there is an additional benefit in that there is no indication of teratogenicity (Teede et al. 2018). Laparoscopic ovarian drilling is another second-line therapy option that can result in a singleton delivery in PCOS patients by reducing the number of follicles. There is no strong proof that it is less effective than other popular ovulation inducing drugs. Laparoscopic ovarian drilling offers no monitoring and low multiple pregnancies risk, but is an invasive surgical procedure with potential decreased reserve and adhesion development risks (Lepine et al. 2017). According to a recent meta-analysis (Abu Hashim et al. 2018), a unilateral operation could be just as successful as bilateral drilling.

### **Metabolic Disorders**

The pertinent on metformin in other groups was evaluated to offer endorsements in light of the gaps in some areas of the evidence in PCOS. According to Teede et al. (2018), metformin acts by elevating glucose absorption in the adipose tissue, skeletal muscle, liver, and ovaries while lowering gluconeogenesis and lipogenesis. It has been shown to help people lose weight and avoid weight gain in various groups, as well as prevent and control gestational diabetes (GDM) and T2DM, as well as lower cardiovascular and microvascular diseases (Naderpoor et al. 2015). Although common, adverse effects frequently have gastrointestinal origins and appear to be self-restricting (Naderpoor et al. 2015). Long-term metformin usage has also raised questions about vitamin B12 insufficiency, although additional study is required. Lower initial doses of metformin, formulations with a prolonged release, and/or administration with food may all help to reduce adverse effects, according to data from different populations (Teede et al. 2018).

According to the most current research, inositol may represent a significant treatment approach for the improvement of PCOS's metabolic features (Gateva et al. 2018). In a similar vein, inositol may likewise

enhance reproductive results. Additionally, inositol appears to be useful in both treating and preventing GDM, while bigger cohort studies are required to fully understand these findings (Gateva et al. 2018).

### **Psychosocial Disorders**

Despite the lack of strong evidence, behavioural changes have been shown to be effective in populations with high cardiometabolic risk, including PCOS patients. Health workers' skill levels might differ, which can make implementation difficult (Moran et al. 2011;Wing et al. 2008).There is a paucity of comprehensive research on food types in PCOS women, but all diets are equally ineffective. Further study is required since there is presently no proof that altering dietary macronutrient composition aids in weight reduction more effectively than traditional dietary methods (Moran et al. 2009).

Some PCOS-related therapies, such as lifestyle changes,insulin sensitizers, and laser therapy have had beneficial benefits on symptoms of depression. These therapies are typically well accepted and have little side effects, allowing women with depression or anxiety disorders to continue receiving them. Women who have been clinically diagnosed with depression or anxiety should also receive treatment in accordance with accepted standards. Future research should concentrate on determining the optimal therapies for this group, who is previously at risk for a number of co-morbidities(Cooney and Dokras 2017).

### **CONCLUSIONS**

PCOS is a complex disorder in which genetic, endocrine, environmental, and behavioural factors are interrelated. It produces a heterogeneous phenotype with reproductive, metabolic, and psychological aspects. This affects females' health and wellness throughout their lives. Physicians should assess and treat patients with PCOS in accordance with their clinical characteristics and risks. To improve all the relatedand discussed outcomes, clinicians should promote lifestyle modifications as the first line of treatment, with special focus on a balanced diet, frequent exercise, and cognitive behavioural therapy. Pharmacological treatment with COCPs and metformin may also be helpful. The same is true for anovulatory infertility; lifestyle changes are advised as the first line of therapy. Letrozole-assisted ovulation induction is the first line of therapy if this doesn't succeed. IVF is only suggested as a last resort if all previous reproductive treatments have failed, in contrast to gonadotrophins and laparoscopic drilling, which are second-line therapy choices. The most recent worldwide evidence-based PCOS guideline offers tools for medical practitioners and PCOS patients to translate and provide a thorough explanation of these therapies. They are intended to work as a unit to assist medical professionals in identifying and treating PCOS-positive individuals with the utmost care.

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