

# Polycystic Ovarian Syndrome (PCOS), A Distress of Female Reproductive Health

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## Abstract

Women of reproductive age are suffering from severe hormonal imbalance due to polycystic ovarian syndrome (PCOS). Clinical manifestations of PCOS are diverse including hyperandrogenism, anovulation, infertility and increased risk of metabolic diseases besides psychosocial dysfunction. Additionally, PCOS leads to various other disturbances such as glucose tolerance, cardiovascular disease, dyslipidemia, obesity and metabolic disturbances. Environmental pollutants and Xenobiotic compounds cause changes in gut microbiota, which further affects metabolism causing metabolic disturbances may lead to PCOS. Various metabolic anomalies resulting from interaction with xenobiotic compounds and environmental pollutants contribute for hormonal imbalance. It is an interlinked vicious circle affected by epigenetic and environmental parameters. Epigenetic approach and molecular analysis of genes involved in PCOS is essential for specific treatment. Biochemical markers like assessment of hormones (hyperandrogenism) and ultrasound (in patients above twenty years of age) used as diagnostic parameters for detection of PCOS. Adopting a healthy lifestyle and minimal exposure to xenobiotic compounds and resetting the disturbed sleep cycle will benefit the patient. Study of molecular markers will help in treating the PCOS in a better manner. This review focuses on important parameters of pathophysiology, which will help in understanding and creating awareness on PCOS.

**Keywords:** Amenorrhea, Anovulation, Endocrine disorder, Epigenetic, Hyperandrogenism, Polycystic ovary syndrome

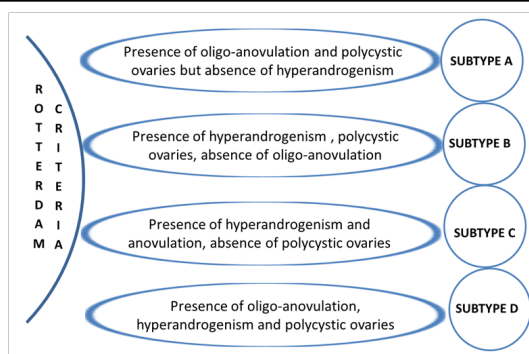
## Introduction

The reproductive health of women is an increased concern these days due to several anomalies related to hormonal imbalance, lack of ovulation, oligomenorrhea, implantation failure resulting in increased infertility rate (Azziz, 2018; Kshetrimayum et al., 2019; Witchelet al., 2019). One such common and frequent disorder related to female reproductive system is polycystic ovarian syndrome (PCOS). PCOS is considered a multifaceted disease with a spectrum of manifestations affecting not only women of childbearing age, but also adolescents and postmenopausal women. It is characterised by imbalance in homeostasis of female reproductive hormones and other

hormones regulating the endocrine loop for reproductive hormone secretion. This in turn creates disturbance in other metabolic pathways, which increases the risk of metabolic syndrome. The metabolic and physiological effect on other systems causes various disorders due to PCOS such as insulin resistance, increased risk of type 2 diabetes mellitus, cardiovascular diseases, dyslipidemia, increased LDL levels, hepatic steatosis (Patel, 2018). The hormonal imbalance also leads to uterine hyperplasia which further can lead to increased risk of uterine cancer as well as ovarian cancer (Gottschau et al., 2015; Ding et al., 2018). Hence, PCOS not only affects the reproductive physiology during reproductive age but also exhibits certain effect during postmenopausal phase. The exact etiology and pathogenesis of PCOS are still an area of active research, although multiple hypotheses have been postulated, ranging from genetic susceptibility to environmental exposure, both in utero and in the postnatal life. Therefore, taking into concern the long-term effect of PCOS, it is necessary to increase the understanding regarding its causes and take preventive measures. Apart from fertility related issues, this disorder increases the dependency on drugs and shows direct effect on neurophysiology causing anxiety, depression, mood swing, low self-esteem due to infertility in females (Azizi Kutenae et al., 2020). The specificity of information regarding causative elements in PCOS can help in increased understanding of its pathogenesis, which will give certain directions for implementing the most effective treatment and management in order to lead a quality life.

### **Diagnostic criteria for PCOS**

The clinical manifestations of PCOS include oligomenorrhoea, hirsutism, excessive acne and hair loss. In adolescence, it causes significant psychiatric disturbances such as anxiety and depression. PCOS is the leading cause of anovulatory infertility in women. The metabolic consequences include impaired glucose tolerance, type 2 diabetes, obesity and increased risk of cardiovascular diseases (Diamanti-Kandarakis and Panidis, 2007). Metabolic complications and increased cardiovascular morbidity are found to be more in the classic PCOS compared to other phenotypes, even after adjustment for obesity. Clinicians now have these criteria to choose from the Rotterdam criteria to be more precise. The Rotterdam criteria for polycystic ovary syndrome (PCOS) used by wide range of medical professionals and researchers is shown in figure 1. The Rotterdam criteria, National institute of health (NIH), Androgen excess PCOS society states the diagnostic features for PCOS (Ganie et. al., 2019). Based on the respective clinical features the diagnosis of PCOS is done. Considering the complexity and variation in clinical features, the PCOS is characterised into different phenotypes such as classic PCOS, Ovulatory PCOS and Normoandrogenic PCOS (Carmina, 2018). The variation in each criterion might interfere with the proper diagnosis. Therefore, to overcome diagnostic pitfalls this new nomenclature proposed which emphasises on clinical and pathological aspects calling it as HA-PODS (Hyperandrogenism and persistent ovarian dysfunction syndrome) (Khadilkar, 2019). This in fact takes into consideration the secondary causes contributing in etiology of PCOS such as insulin resistance, endometrial hyperplasia, hypertension, obesity, thyroid disorders, etc. (Khadilkar, 2019).



**Figure 1** The Rotterdam criteria for polycystic ovary syndrome (PCOS) used by a wide range of medical professionals and researchers. doi:10.1093/humrep/des424(Rotterdam ESHRE/ASRM-Sponsored PCOS consensusworkshop group, 2004)

## Incidence of PCOS

The incidence of PCOS has been carried out in various populations over the globe. At the global level, the incidence of PCOS is about 15-20% according to the study carried out by Patel in 2018. The study carried out in 2008 by Allahabadia and Merchant, the incidence of PCOS reported in Indian subcontinent was 5-10%. However, a recent study states the incidence of PCOS to be 21.05% in India (Aggarwal et al., 2019). This prevalence rate observed among medical students of age group 17-24 from Mumbai. Another study indicates the prevalence to be 3.7 -22.5% within India (Ganie et al., 2019). The broad-spectrum range in prevalence may be due to the lifestyle of urban or rural pattern and the criteria used to diagnose the PCOS. Different regions showed varied prevalence such as Bengaluru (9.13% in 2011), Lucknow (3.7% in 2012), Mumbai (22.5% in 2014), Tamil Nadu (18% in 2015), Karnataka (9.1% in 2016) and Chennai (6% in 2017) according to the study carried out by Ganie et al., in 2019. The prevalence rate from Mumbai, Tamil Nadu, Bengaluru and Chennai were calculated based on fulfilling Rotterdam criteria while the Lucknow and Karnataka states prevalence was based on NIH and modified version of Cronin questionnaire respectively. Study from each region is necessary to understand the prevalence in correlation to the lifestyle factors and environmental parameters. This can help in creating awareness and implementing certain habits to avoid the occurrence of PCOS in young females.

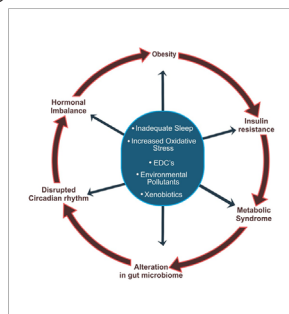
## Pathophysiology of PCOS

The female reproductive hormones level is disturbed in PCOS leading to anovulation, oligo-ovulation, amenorrhea, oligomenorrhoea, hyperandrogenism and polycystic ovarian morphology. The estrogen level is increased and progesterone level is decreased. Simultaneously increased Anti Mullerian hormone (AMH) and Prolactin (PRL) levels totally alters the pituitary – ovarian endocrine loop (Rao and Homburg, 2018; Khadilkar, 2019). This mainly occurs due to disturbances in steroidogenesis pathway of androgens occurring in thecal cells of ovaries. The excessive androgen is a result of hyperstimulation of thecal cells by high level of Luteinizing hormone (LH). Due to low progesterone, the endometrial receptivity that is affected leads to infertility apart from anovulation (Benangiano et al., 2018). This is due to decreased Follicle stimulating hormone (FSH) levels that affect the ability of granulosa cells to synthesize progesterone. Decrease in FSH levels is due to inhibitory action of AMH and lack of LH pulsatile surge that in turn leads to anovulation/ oligoovulation, which causes the graffian follicle to gain fluid and get converted into a cyst (Rao and Homburg 2018). Accumulation of several cysts leads to polycystic ovarian morphology. In PCOS,

the progesterone resistance observed leads to oligomenorrhea / amenorrhea (Benagianoet. al., 2018). The increased PRL hormone further interferes with the levels of Gonadotrophin-releasing hormone (GnRH) (Patel, 2018). Excessive androgens contribute in metabolic disorders such as impairment in function of pancreatic  $\beta$  cells, enhancing intra-abdominal adipocytes hypertrophy (Condorelli et al., 2018). Metabolic alterations due to metabolic syndrome, insulin resistance leads to increase the etiology of PCOS. A supporting study shows the prevalence of metabolic syndrome to be 19.1% and that of insulin resistance was 14.1% in Chinese women suffering from PCOS (Li et al., 2014).

Additionally, genetic and environmental factors have also been found to contribute in pathogenesis of PCOS. Alterations in gene expression have been proved a potent contributor for disturbances in female reproductive physiology. PCOS is a highly inherited complex polygenic, multifactorial disorder. Numerous candidate genes have been studied, largely through association studies, using a candidate gene approach, transmission disequilibrium test (family based association), or genome-wide association study. Of note, genome-wide association studies have identified loci (regions on chromosomes) that are of interest. Candidate genes suggested by such genome-wide association studies have been found to be related to gonadotropin action, ovarian follicle development, insulin action, and organ growth (Mykhalchenko et al., 2017).

Various studies have proved the interference of environmental pollutants and other xenobiotic compounds causing metabolic disturbances and inducing insulin resistance in variety of tissues (Palioura and Diamanti-kandarakis, 2015). As shown in the figure 2, various parameters such as inadequate sleep, increased oxidative stress, interaction of endocrine disrupting chemicals (EDC's), environmental pollutants and xenobiotics at genetic level alter the expression of genes further affecting the hormonal loop by inducing obesity, insulin resistance, metabolic syndrome, alteration in gut microbiome, disrupted circadian rhythm. Thus, an interdependent vicious circle of anomalies is set leading to pathogenesis of PCOS.



**Figure 2** Pathogenesis of PCOS: An interdependent vicious circle of various anomalies like Obesity, Insulin resistance, metabolic syndrome, change in gut biota, altered circadian rhythm and hormonal imbalance are recognized in pathogenesis of PCOS.

At the hypothalamic–pituitary level, patients with PCOS demonstrate gonadotropin secretory abnormalities, including increased LH pulse amplitude and frequency, and increased circulating levels of LH, most evident in patients who are not obese. In addition, the hypothalamic–pituitary axis appears to be somewhat resistant to the suppressive effects of progesterone on gonadotropin-releasing hormone pulse frequency (Azziz et al., 2016).

## Management of PCOS

Precise cure for PCOS is not yet available but medications will help in decreasing or to some extent reversing the effects of a particular etiology. The normal levels of female reproductive

hormones are maintained by administration of birth control pills (Patel, 2018; Louwers and Laven 2020). This helps in replacement of progesterone and estrogen in an exogenous manner where their presence will reduce the stress on pituitary – ovarian endocrine loop in turn balancing the hormones level. Metformin acts a good insulin sensitizer; it helping in reducing insulin resistance and improves progesterone resistance (Homburg, 2014; Benangiano et al., 2018). Flutamide also effectively reduces the insulin resistance in PCOS females (Condorelli et al., 2018). Finasteride drug administration reverses the effect caused due to hyperandrogenism such as baldness and excessive facial growth (Geller et al., 2011). Spironolactone also helps in reducing androgens and controlling acne outbreak caused due to it (Geller et al., 2011). Clomifene citrate used to induce ovulation in anovulatory females works by blocking hypothalamus and pituitary estrogen receptors in turn inducing discharge of FSH leading to successful ovulation (Homburg, 2014). Letrozole is also used to induce ovulation and is more potent than Clomifene and it acts as aromatase inhibitor and blocks conversion of androgens to estrogen (Homburg, 2014). Vitamin D administration in PCOS have proved to decrease serum androgens (androstenedione and testosterone) and increasing insulin sensitivity (Karadag et al., 2018). Administration of statins has proved effective in reducing androgens, decreasing ovarian size and impairment in menstrual cycle (Ortega and Duleba, 2014). Statins are also effective in improving lipid profile and decreasing the risk of cardiovascular diseases (Ortega and Duleba, 2014). Cabergoline and dopamine agonists can reverse hyperprolactinemia (Khadilkar, 2019). Alternatively, Bariatric surgery has proved to be effective in improving hyperandrogenism and menstrual irregularities in PCOS patients. It also helps in weight loss and improvement in some markers of dyslipidaemia such as triglycerides, HDL-C, VLDL-C (Christ and Falcone, 2018). Management of stress using meditation can improve the quality of sleep in PCOS females.

Apart from medications, lifestyle modification can nullify the effect of PCOS for long term and will help in decreasing the drug dependency. Lifestyle modifications include protein-based diet, adequate carbohydrate consumption and regular exercise that can help in reducing the insulin resistance and improve anovulation (Geller et al., 2011). Weight loss by opting hypocaloric diet by omitting glycosylated end products can prove to be successful in reversing etiology of PCOS (Geller et al., 2011; Pasquali, 2018). Decreased use of cosmetics and fragrant products can help in reducing hormonal imbalance because certain components in cosmetic products such as Parabens, 1,4-dichlorobenzene (Aker et al., 2016) act as endocrine disrupters. Bisphenol A (BPA) found in plastics also shows a role of reproductive and endocrine modulator (Palioura and Diamanti-Kandarakis, 2015). Therefore, avoiding the use of plastic containers to store food and water can prevent the consumption of BPA.

## Conclusion

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in reproductive-aged women. The adverse effect of PCOS not only seen in reducing the reproductive ability but also exhibits adverse effects on psychology of females (Pasquali, 2018; Azizi Kutenae et al., 2020). It causes anxiety, depression and low self-esteem in females, which further alters the sleep cycle causing sleep related disorders. The disease related changes in body such as obesity, acne, facial hair can induce body shaming leading to low life which shows direct effect on individual's performance. This can further cause negative effect on sleep (Azizi Kutenae et al., 2020). A long term insulin resistance due to PCOS can increase the risk of type 2 diabetes mellitus (Irgam et al., 2019), where the patients in later life have a high risk of developing Alzheimer (Paul et al., 2018; Yegambaram et al., 2015). This long-term effect of PCOS ends up disturbing the quality of one's life, which in turn leads to various disorders. Unhealthy lifestyle can amplify the effect and the



incidence of PCOS. Finally, to conclude awareness among young females is crucial in order to help them overcome PCOS effectively. However, timely correct diagnosis coupled with genetic and molecular studies may help broaden the view regarding pathogenesis of PCOS, which in turn may help in designing a highly effective treatment for PCOS.

### **No Conflicts of Interest**

### **Source of Funding: Self**

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