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## Polycystic ovary syndrome (multifactorial endocrinopathy): manifestation and treatment strategies

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### Abstract

Polycystic ovary syndrome is a disorder featuring poor ovarian health and hormonal imbalance as its primary characteristics. This disorder disturbs the three basic aspects of life - physical, mental, and social health due to the changes in the normal functioning of organs and depression associated with low self-esteem. However, detection of this syndrome is a difficult task due to its common symptoms and hence must be excluded from the disorders with similar manifestations like idiopathic hyperandrogenism and diabetes. It is a multifactorial endocrinopathy, and a single symptom is having the potential to lead to other health issues. Whereas, high amounts of androgens consequently lead to hirsutism, disordered folliculogenesis, and dyslipidemia. Infertility, an additional health issue associated with polycystic ovary syndrome commonly found in females these days is also linked to poor lifestyle habits like less exercise and diets rich in fat and sugar. Although, various treatments including chemical drugs and herbal therapies aid in curing hormonal imbalances. However, trust towards the utility of herbs is still a preferred option due to fewer side effects and easy availability in the locality. A few chemical drugs like bicalutamide and flutamide impart an anti-androgenic effect on the body to cure the syndrome but also have a bad effect on liver health. The present review of literature puts forward information about polycystic ovary syndrome and its clinical manifestations, along with the management of the syndrome.

**Keywords:** Polycystic ovary syndrome, endocrinopathy, manifestations, management, lifestyle

### Introduction

Polycystic Ovary Syndrome (PCOS), a complex hormonal disorder is a concerning consequence of modern-day lifestyle as well as nutritional and environmental factors. Although, it is reversible condition but also considered one of the major contributors to lifestyle-related chronic disorders. The mentioned endocrinopathy has affected the lives of over 200 million women of reproductive age worldwide (Parker *et al.*, 2022) <sup>[1]</sup>. The presence of Polycystic Ovary Syndrome (PCOS) is recognized by the presence of two key features includes irregularity in menstruation and hyperandrogenism. The latter term is a condition with increased testosterone levels in the female body. However, these characteristics can be seen with or without changes in ovarian morphology. PCOS is highly related to the concept of insulin resistance which further leads to metabolic and cardiovascular disorders (Mukerjee, 2019) <sup>[2]</sup>. Stein and Leventhal, American gynecologists were first to bring out the actual picture of this syndrome in 1935. Before this the concept of PCOS was unclear. They further described the syndrome on three bases including hyperandrogenism, multiple cysts in the ovaries, and amenorrhea. Thus, polycystic ovary syndrome is also referred to as “Stein and Leventhal syndrome” (Azziz, 2021) <sup>[3]</sup>. Further progress in the exploration of the syndrome was made through the introduction of diagnostic criteria, like the National Institute of Health (1990), Rotterdam (2003) <sup>[63]</sup>, and the androgen excess society (AES) criterion in 2006 (Hoeger *et al.*, 2021) <sup>[4]</sup>.

Several cardiometabolic conditions like hypertension, as well as conditions like dyslipidemia and infertility, are closely associated with PCOS. Moreover, other symptoms like insulin resistance and hyperinsulinemia make the body more vulnerable to health issues like type 2 diabetes mellitus. Additionally, girls suffering from type 2 diabetes mellitus and PCOS are more likely to face depression (Cionna *et al.*, 2022) <sup>[5]</sup>. However, PCOS is also responsible to affect mental health because of its clinical manifestation. Hirsutism, alopecia, and acne are the symptoms that affect the appearance of a person which lowers the self-esteem of women resulting in depression.

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Thus, with the rise in the cases of PCOS, a rise in depression is also evident (Xing *et al.*, 2022) [8].

Although, the treatment strategy of PCOS requires strong willpower as it demands a positive lifestyle change, physical activity for half an hour per day, and a quality value-added diet. Sometimes, drugs like metformin or spironolactone are also required if the problems like insulin resistance and excess androgen concentration are at a peak in the body (Meczekalski *et al.*, 2023) [9].

### Prevalence

The prevalence of PCOS varies according to different diagnostic criteria. According to the standards of the National Institutes of Health (NIH) criteria, the prevalence of PCOS is reported as approximately 6% globally, however, whereas the prevalence is stated as 10% based on the criteria such as Rotterdam or androgen excess or polycystic ovary syndrome society (AE-PCOS Society) (Rajashekar *et al.*, 2022) [10]. Although, PCOS affected around 5-10% of the female population falling in the reproductive phase, while 4-8% of middle-aged as well as young females are affected in the United States of America (Bozdogan *et al.*, 2016) [11].

The prevalence in adolescents aged 15-19 years was 22.6% according to the Rotterdam criterion, while the value dropped to 9.8% as per the criteria formulated by the androgen excess and polycystic ovary syndrome society. The prevalence of PCOS in Thailand at 5.29% was reported as significantly lower than in Iran at 8.3 - 11.4% (Naz *et al.*, 2019) [12]. Whereas, factors like environmental conditions and genetic makeup also have an indirect effect on the prevalence rate (Zafar *et al.*, 2019) [13].

Ganie *et al.*, (2020) [14], investigated that the prevalence rate varied among Asian nations. Although, the prevalence of PCOS was found to be 15.2% in Iran followed by 6.3% in Sri Lanka, 5.6% in China, and 5.3% in Thailand respectively. However, Indian women were found to be more affected by PCOS with a prevalence rate of 36% (especially, the adolescents falling in the age group of 17-19 years). Further, it was observed that the prevalence rate was higher when Rotterdam and androgen excess society (AES) criteria were followed.

### Diagnosis

The first diagnostic criteria for PCOS was given by the National Institutes of Health (NIH) in 1990. However, in 2003 a new diagnostic criteria was introduced in a workshop conducted in Rotterdam, called Rotterdam Criteria. This criterion focuses on three clinical manifestations of PCOS, among which two must be confirmed present in the body. These three conditions are, anovulation or oligomenorrhea, hyperandrogenism, and polycystic ovaries (12 cysts in the ovaries measuring 2-9mm) (Witchel *et al.*, 2019) [15]. Further, this criterion came up with the modification in 2006 by the androgen excess society (AES), which required the presence of hyperandrogenism with anovulation/ oligomenorrhea or multiple cysts in the ovary for the confirmation of PCOS (Deswal *et al.*, 2020) [16]. PCOS is also caused due to heritable genetic factors, however, the genetically distinct phenotypes remained less focused area by several diagnostic criteria (Chang and Dunaif, 2021) [17].

Characteristics of puberty in girls and the features of PCOS are quite similar and therefore the diagnostic criteria for adults are not meant for the diagnosis in adolescent girls. Furthermore, other disorders closely associated with hyperandrogenism must be distinguished by diagnostic

measures in PCOS conditions. Irregular menstruation and excessive androgen production, in adolescent girls at least after two years of menarche are the major diagnostic criteria and are considered to the category of high risk for PCOS (Witchel *et al.*, 2019) [15].

### Etiology of PCOS

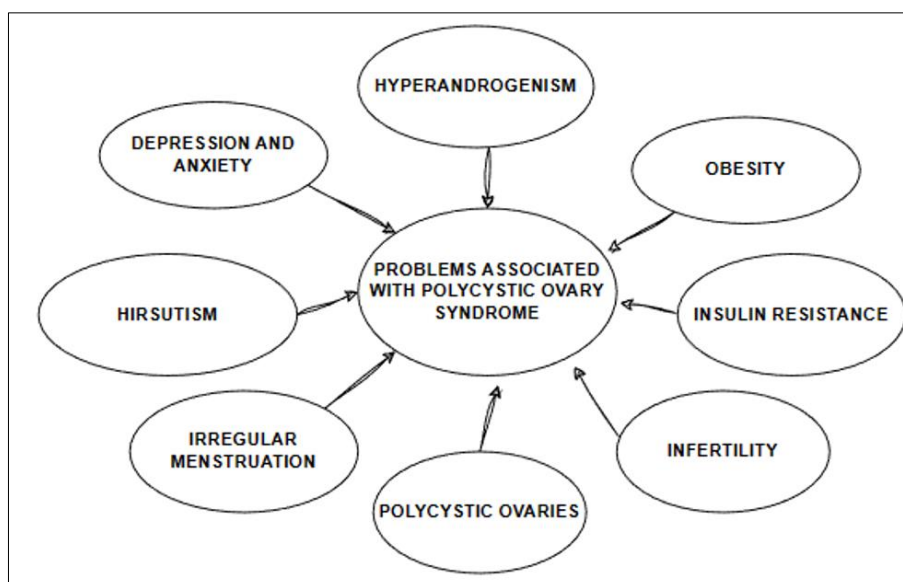
Environmental, as well as family history, are some of the major causes of PCOS. Additionally, the risk can be increased due to bad lifestyle habits, poor diet, and infectious agents. Insulin resistance is the secondary factor, which disturbs the usual functioning of ovaries, and consequently leads to higher levels of male hormones. On the other hand, genetic modification is also considered as a contributory cause of PCOS. Changes in the nucleotides lead to problems during the transcription of the gene which leads to develop PCOS (Ajmal *et al.*, 2019) [6]. Moreover, disturbance in the formation of reproductive hormones and their action leads to excessive ovarian androgen production. While, the reduction in the sex hormone binding globulin in the liver, eventually results in hyperandrogenism. Some of the secondary contributory factors which have a vice-versa aspect on PCOS include obesity, depression, irregular menstruation, and insulin resistance (Lim *et al.*, 2019) [7].

### Clinical Manifestations

The clinical features of PCOS can be seen at different stages of the reproductive phase. Although, some women experience the symptoms on the first menstruation only, while some may get an indication of this disorder after sudden weight gain, excessive facial growth, and difficulty in conception. There are several symptoms of this syndrome, but three major to be considered are, multiple cysts in the ovaries, excessive testosterone levels, and irregular menstruation (Mukerjee, 2019) [2]. Distinguishing the symptoms of PCOS from other health issues like diabetes, nutritional deficiencies, fibroids, endometrial cancer, and infertility is a critical task. The symptoms of the above-mentioned health issues overlap with the condition of PCOS. Moreover, the fluctuations in menstruation can't always be considered a symptom of PCOS, may be it is due to menarche or some nutritional deficiencies in the body, for instance, iron deficiency. The problem of heavy blood flow may be due to fibroid and endometrial cancer and thus the overlapping of PCOS symptoms with other disorders is very common and needs a thorough detection (Sherif *et al.*, 2021) [20]. The common health disorders that are associated with PCOS are shown in (fig 1).

### Obesity

Obesity is a condition in which the body deposits excessive fat in various body tissues which can potentially lead to health issues like fatty liver disease, hypertension, osteoarthritis, myocardial infarction, and stroke (Blucher *et al.*, 2019) [22]. Although, around 80% of the affected population faces the problem of obesity. However, the severe depression caused due to the increased levels of cortisol as the appearance of a woman gets affected which further leads to develop low self-esteem (Butler *et al.*, 2019) [21]. On the other hand, cortisol further causes excessive secretion of glucocorticoids, responsible for the deposition of fat in the visceral and intra-abdominal areas. Furthermore, it invites health problems like metabolic disorders, and hence the whole body system gets disturbed (Maya *et al.*, 2020) [19].



**Fig 1:** Problems associated with polycystic ovary syndrome

### Insulin resistance

The concept of insulin resistance is not universal in PCOS. Although, abnormal levels of insulin disrupt the process of ovulation and hence fertilization becomes difficult in such cases. The combination of insulin with the luteinizing hormone (LH) and sometimes with insulin growth factor (IGF) disturbs the normal formation of follicles in the ovary (Zeng *et al.*, 2020) [23]. However, the increased levels of insulin result in the higher production of vascular endothelial growth factor (VEGF), a major compound required in the process of angiogenesis in the developing embryo. Moreover, insulin resistance can also alter the duration as well as the blood flow during menstruation (Apte *et al.*, 2019) [24]. However, higher levels of vascular endothelial growth factor boost the production of androgen, thus disturbing the hormonal balance and also the functioning of reproductive systems (Bou *et al.*, 2018) [25].

### Hyperandrogenism

A condition in which the levels of androgens exceed the usual value in the female body and is one of the significant symptoms of PCOS (Ashraf *et al.*, 2019) [27]. Although, male hormones are also released in the female body but in trace amounts. While, in the case of hyperandrogenism, excessive production takes place in the theca cells of the ovary. Hyperinsulinemia is another factor contributing to excess androgens by increasing the levels of free testosterone levels, hence decreasing the concentration of sex hormone binding globulin (SHBG) (Abhinaya *et al.*, 2019) [26]. The presence of excessive male hormones in the female body leads to the development of masculine characteristics like uncontrolled growth of terminal hair throughout the body especially the face, areola, and genitals. The measurement of free testosterone and the sex hormone-binding globulin should be done very carefully in order to get free androgen index (FAI) (Armanini *et al.*, 2022) [28].

### Infertility

PCOS not only disturbs metabolic functioning but also affects fertility in women by influencing ovarian morphology or by disrupting the hormonal balance of the body (Cena *et al.*, 2020) [29]. Problems like irregular menstruation and

anovulation disturb the normal functioning of the reproductive system of the female, thus making conception more difficult. Moreover, if pregnancy happens, then the continuity becomes tough due to improper or weak endometrial lining. While, endometrial cancer is also one of the side effects of PCOS (Zehravi *et al.*, 2021) [30]. However, follicular development gets disturbed due to higher levels of anti-mullerian hormone (AMH) which resists the development of follicles (Kriedt *et al.*, 2019) [31]. The anti-mullerian hormone keeps a check on the growing follicles, thus its optimum levels are a must to initiate gestation as well as maintenance of a healthy pregnancy (Clemente *et al.*, 2021) [32].

### Irregular menstruation

Regular menstruation is an indicator of a healthy reproductive system that initiates at the time of puberty. However, the fluctuations in the menstruation cycle during menarche must be distinguished from the symptoms of PCOS. Although, any sort of disturbance like changes in the cycle patterns and menstrual flow may be a representative of many health issues like metabolic disorders (insulin resistance, dyslipidemia, etc), and hormonal imbalance further leads to PCOS (Park *et al.*, 2021) [33]. Irregularity in the menstrual cycle is not only caused by hormonal imbalance, nutritional deficiencies standouts as the other prominent reason. Anovulation (no ovulation) or oligoovulation (infrequent or irregular ovulation) can be the possible causes of irregular menstruation. Other clinical manifestations like hirsutism (excessive hair growth on areas like the face, and chest), weight gain, depression, mood swings, sleep problems, and fatigue are also common symptoms of polycystic ovary syndrome (Witchel *et al.*, 2020) [34].

### Hirsutism

Hirsutism is referred to as excessive unwanted hair growth on the female body, characteristically similar as male body due to the higher production of androgens in the female body. Idiopathic hyperandrogenism and PCOS account for more than 85% of hirsutism cases (Matheson and Bain, 2019) [35]. Excessive unwanted hair growth can be seen on the face, breast areola, inner thighs, chest, and linea-alba which are

androgen-sensitive sites in the body. Among the three types of hair, lanugo, vellus, and terminal hair, the latter is the characteristic feature of hirsutism. However, the terminal hair is longer, pigmented, and thick as compared to lanugo (which covers the fetal body and disappears after some time) and vellus (fine thin hair) (Spritzer *et al.*, 2022) [36].

### Polycystic ovaries

Polycystic ovarian morphology is one of the major problems associated with PCOS. It is characterized by the presence of more than 12 antral follicles in each ovary according to the Rotterdam criteria. (Gao *et al.*, 2020) [37]. The intraovarian disturbance is also due to the scarcity of enzyme aromatase, which produces estrogen from the androgen. Furthermore, follicular development as well as ovarian morphology gets disrupted by the increased levels of testosterone. (Shamsi *et al.*, 2020) [38].

### Depression and anxiety

Several studies have confirmed that sufferers of PCOS face the problem of depression as they lose their self-esteem due to changes in their appearance. Depression and obesity are interlinked as both factors have an interchangeable effect. If any one of these two factors increases it will consequently lead to a rise in the other factor and hence have a vice-versa effect on each other. Hirsutism, infertility, social anxiety, obsessive-compulsive disorders, etc. are among the common characteristics of PCOS that might be contributing to anxiety and depression in the patients (Sabir *et al.*, 2021) [39]. Thus, this syndrome not only affects physical health but also spoils the quality of health by disturbing mental health. Hence, the patients are more likely to face the issues of mood swings due to continuous and frequent hormonal changes in the body, (Zehravi *et al.*, 2021) [30].

### Treatment strategies and approaches

Different treatment strategies for PCOS treatments include allopathic, homeopathic as well as herbal approaches. Each of the above-mentioned ways employs particular drugs and herbal components which aid in normalizing the hormonal system of the body.

#### Allopathic approach

Following are the various drugs utilized to treat PCOS like metformin, inositol, bicalutamide, flutamide, spironolactone, etc.

#### Metformin

Metformin is one of the most common drugs utilized for diabetes as well as PCOS due to its tolerability with limited side effects. Metformin is responsible to alleviate insulin resistance, a metabolic condition common to type 2 diabetes mellitus and PCOS patients. However, it also aids in the improvement of lipid profile by increasing the concentration of high-density lipoprotein while lowering the concentration of triglycerides (Cignarella *et al.*, 2020) [41]. The benefits of metformin are not only limited to hyperinsulinemia but also help to maintain the disrupted functioning of the reproductive system. Moreover, it has been observed that metformin improves the rate of ovulation, and pregnancy due to its anti-inflammatory effect (Duan *et al.*, 2021) [42].

#### Inositols

Inositol, an essential chemical compound, mainly present in two isomeric forms “Myo-inositol” and “D-chiro inositol”. These work as an aid in the process of follicle formation, and the signaling of insulin. The balance between these two isomers maintains the normal functioning of ovaries and proper hormonal secretion, and hence the presence in optimum amounts is important. Along with improving reproductive health, inositol is also helpful to maintain metabolic health (Kamenov and Gateva, 2020) [43]. Several nutraceutical inventions are introduced keeping in view the benefits provided by the inositol on particular clinical manifestations like anovulation, irregular menstruation, and insulin resistance. However, the compound is naturally present in citrus fruits and vegetables (Davinelli *et al.*, 2020) [44].

#### Bicalutamide

Bicalutamide is an anti-androgen drug that aids in dealing with female pattern hair loss, one of the significant clinical symptoms of PCOS. It also lowers the symptoms like acne and hirsutism caused due to the higher concentration of androgens secretion in the female body and is considered safe than flutamide (an antiandrogen drug) (Nieto *et al.*, 2020) [45]. Furthermore, anti-androgens block the activity of androgen receptors by acting as an antagonist. Although, bicalutamide is not a much-preferred drug because of its toxic effect on the liver (Cardozo and Romero, 2021) [46].

#### Flutamide

Flutamide, is a drug that belongs to the class of anti-androgen category and hence acts mainly on the higher concentration of androgens. It is used widely to treat problems like acne, hirsutism, hyperandrogenism, and tumors in the prostate gland. Flutamide is known to have fewer side effects but is considered a hepatotoxic drug (Johnson and Sonthalia, 2021) [47]. Flutamide competitively binds with the androgen binding receptors to block the attachment of androgens in the target tissues and hence was considered to have a potent anti-androgen characteristics (Anastassakis, 2022) [48].

#### Spironolactone

Spironolactone is an anti-androgen chemical drug that serves as a better alternative to combined oral contraceptives with fewer side effects (Rajashekar *et al.*, 2022) [49]. Spironolactone also aids to maintain hepatic, and ovarian tissue damage by altering the levels of higher uric acid levels and triglyceride accumulation. It reverses increased luteinizing hormone levels and decreased follicle-stimulating hormone back to normal for better follicular development (Adeyanju *et al.*, 2020) [50].

#### Herbal approach

The trust in herbal medications to treat various hormonal disorders like diabetes and PCOS is much stronger as compared to the standard medicines. This fact can be attributed to the fewer side effects of the herbs. Hence plants with medicinal importance like *Cinnamomum zeylanicum*, *Mentha spicata*, *Saraka indica*, and *Withania somnifera* have the potential to deal with hormonal imbalance (Pachiappan *et al.*, 2020) [51].

Although, traditional/herbal medicines not only play a curative role but also have a rehabilitative effect and prevent a hormonal imbalance. The bioactive compounds present in the nutritional profiles of herbs provide numerous benefits like

boosting immunity and lowering cholesterol levels other than treating disorders (Khanage *et al.*, 2019) [52]. Several studies related to the use of herbs for PCOS have already taken place are mentioned in (Table 1).

**Table 1:** Utilization of herbs for treatment of PCOS

Herb	Part used	Benefits	References
<i>Cinnamomum zeylanicum</i>	Bark	Lowers cholesterol Improves HDL levels	Maleki <i>et al.</i> , 2021 [53]
<i>Camellia sinensis</i>	Leaves	Lowers weight Lowers fasting insulin	Jazani <i>et al.</i> , 2019 [54]
<i>Trigonella foenum-graecum</i>	Seeds	Improves FSH levels Reduces cyst size	Yadav <i>et al.</i> , 2020 [55]
<i>Mentha spicata</i>	Leaves	Lowers free testosterone Reduces hirsutism	Ainechi <i>et al.</i> , 2019 [64]
<i>Aloe vera barbadensis</i>	gel	Lowers hyperandrogenism Improves menstrual cycles	Ashkar <i>et al.</i> , 2020 [57]
<i>Grifola frondosa</i>	Whole herb	Improves ovulation	Jazani <i>et al.</i> , 2019 [54]
<i>Panax ginseng</i>	Root	Improves follicle stimulating hormone levels	Yadav <i>et al.</i> , 2020 [55]
<i>Cinnamomum verum</i>	Bark	Improved folliculogenesis	Maleki <i>et al.</i> , 2021 [53]
<i>Foeniculum vulgare</i>	Seeds	Reduces testosterone levels	Ashkar <i>et al.</i> , 2020 [57]
<i>Cimicifuga racemosa</i>	Rhizome	Improves endometrial thickness	Jazani <i>et al.</i> , 2019 [54]
<i>Tribulus terrestris</i>	Vine	Improves ovulation	Yadav <i>et al.</i> , 2020 [55]

### Lifestyle modifications

Changes in the lifestyle are regarded as the core components of PCOS management. However, its benefits are not only limited to the improvement in physical health but also contribute to the betterment of social and mental health (Aly *et al.*, 2021) [58].

### Dietary approach

An unhealthy or poor diet is one of the major reasons for metabolic disorders because it is rich in sugar and fat. However, the drawbacks are not only limited to metabolic disorder but also affects the normal functioning of the stomach and spleen. In some cases, a poor diet can also cause blood stagnation in the ovarian and uterine tissues leading to irregular menstruation (Che *et al.*, 2021) [59]. Macronutrients have a noticeable role in maintaining health. While, switching to a low-fat low sugar diet from a high-fat high sugar diet helps to alleviate total cholesterol levels and to treat insulin resistance (Paris *et al.*, 2020) [61]. Therefore, opting for good food habits followed by lifestyle changes is required especially in obese conditions in PCOS patients.

### Physical activity approach

Exercise and behavioral therapy are the key factors of the modified lifestyles as regular exercise helps in lowering cholesterol and triglyceride levels. Practicing yoga, gym, and aerobic exercises like dance, spinning, boxing etc. in regularity helps to lower the testosterone levels (Kim and Lee, 2022) [60]. Although, exercise can improve the uptake of glucose by the cells (especially skeletal cells) where it is used as energy and hence controlling the increased blood sugar levels in the blood (Barber *et al.*, 2019) [62]. While, basic problems associated with PCOS like weight gain, increased insulin levels, and poor lipid profile can be cured by performing physical activity.

### Conclusion

PCOS, an alarming disorder affects mainly the women falling in reproductive age. Although, a sedentary lifestyle and an unhealthy diet are the major contributors to the acceleration of PCOS. There are various ways out to overcome the symptoms of PCOS, however, its safety and possible side effects need more studies to be done for better clarification of the concept.

Moreover, limited awareness regarding modifications that can bring huge changes in the life of PCOS patients is another aspect that needs attention. Thus, health professionals need to work on planning to create a clearer picture of PCOS in the community.

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