# The Polycystic Ovary Syndrome (PCOS)

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**Abstract**

PCOS is the commonest endocrine abnormality in women of reproductive age. It represents the major cause of anovulatory infertility and is also associated with hirsutism and acne. The typical biochemical features are elevated serum levels of testosterone and luteinizing hormone (LH) along with metabolic disturbances

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including insulin resistance and abnormalities of energy expenditure. PCOS is now recognized as a major risk factor for the development of type 2 diabetes (T2DM) and cardiovascular disease in later life. At least in part, this reflects the strong associations between PCOS and obesity, with the latter being an amplifier of PCOS.

The etiology of PCOS is unclear, and it seems to be a complex disease resulting from a complex interplay between genetic and environmental factors. Moreover, there is evidence for familial clustering of endocrine and metabolic features of PCOS. Environmental factors such as diet and obesity might similarly contribute to the phenotype. Due to its heterogeneous nature, there have been historical disagreements about the definitions and how to diagnose PCOS.

Treatment should be tailored to the complaints and needs of the patient and involve restoring fertility, treatment of metabolic complaints, treatment of androgen excess, and providing endometrial protection.

The complexity of the disorder, and the impact on quality of life, requires timely diagnosis, screening for complications, and management strategies of the long-term health issues associated with PCOS. The syndrome remains underdiagnosed, and women experience significant delays to diagnosis.

**Keywords**

Polycystic ovary syndrome (PCOS) · Oligomenorrhea · Amenorrhea · Anovulation · Hyperandrogenism · Polycystic ovarian morphology (PCOM) · Hirsutism · Ovulation induction · Medical treatment · Health risks

## Introduction

Polycystic ovary syndrome (PCOS) is a significant public health issue with reproductive, metabolic, and psychological features. PCOS is the most common endocrine disease affecting 5–20% of reproductive-aged women with up to 70% of affected women remaining undiagnosed (Azziz et al. 2016; Teede et al. 2018). Presentation varies by ethnicity, and the prevalence of more complete phenotypes in PCOS was higher in subjects identified in referral versus unselected populations, suggesting the presence of significant referral bias (Lizneva et al. 2016). Women with PCOS present with diverse features including psychological issues such as anxiety, depression, and disturbed bodily images. Moreover, PCOS is associated with reproductive disorders such as irregular menstrual cycles, hirsutism, infertility, and pregnancy complications. Finally, metabolic features such as insulin resistance, metabolic syndrome, prediabetes, type 2 diabetes, and several cardiovascular risk factors are also associated with the syndrome (Teede et al. 2018). PCOS is a diagnosis of exclusion, based primarily on the presence of hyperandrogenism, ovulatory dysfunction, and PCOM.

Treatment should be tailored to the complaints and needs of the patient and involves induction of ovulation in order to restore fertility either by oral drugs or

by administering gonadotropins. Treatment targeting metabolic abnormalities includes lifestyle changes, medication, and potential surgery for the prevention and management of excess weight. In case restoring fertility is not the ultimate goal, androgen suppression to treat hirsutism and/or alopecia as well as providing endometrial protection in order to avoid endometrial cancer is a necessity. Last but not least, physicians should pay more attention to the detection and treatment of psychological features associated with the syndrome (Azziz et al. 2016; Teede et al. 2018).

The complexity of the disorder, and the impact on quality of life, requires timely diagnosis, screening for complications, and management strategies of the long-term health complications such as type 2 diabetes mellitus (T2DM), hypertension, and possibly cardiovascular disease. This is especially important since PCOS remains underdiagnosed and women experience significant delays to diagnosis (Neven et al. 2018).

## Diagnostic Features

The diagnosis of PCOS remains a controversial issue with challenges defining individual components within the diagnostic criteria, significant clinical heterogeneity generating a range of phenotypes with or without obesity, ethnic differences, and variation in clinical features across the life course (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group 2004). This culminates in delayed diagnosis, poor diagnosis experience, and dissatisfaction with care reported by women internationally. These challenges are exacerbated by a lack of recognition of the diverse features of PCOS, inadequate research, and a lack of comprehensive international evidence-based guidelines (Teede et al. 2018).

The Rotterdam criteria for PCOS have been endorsed by the National Institutes of Health (NIH) (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group 2004). There is a general agreement that the diagnosis of PCOS must be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries (PCOM). Moreover, other disorders that might mimic these clinical features of PCOS are to be excluded. These include thyroid disease, hyperprolactinemia, and nonclassical congenital adrenal hyperplasia (Legro et al. 2013). The Androgen Excess Society emphasizes the importance of clinical and/or biochemical hyperandrogenism and places less importance on polycystic ovary morphology (PCOM) (Goodman et al. 2015). However, the most recent consensus meeting endorsed by the NIH has decided that for clinical purposes the Rotterdam criteria should be used.

### Irregular Menstrual Cycles

Ovulatory dysfunction is a key diagnostic feature of PCOS with irregular menstrual cycles reflecting ovulatory dysfunction, as reflected in the Rotterdam criteria. If the

interval between two consecutive menses exceeds 35 days, it can be assumed that chronic anovulation is present. Such cycle intervals are generally referred to as oligomenorrhea. However, if the interval between subsequent menstrual bleedings is only slightly longer than normal (ranging from 32 to 35 days), or if cycles are slightly irregular, ranging from 32 to 35 to 36 days, ovulation should be assessed (Goodman et al. 2015). Several studies have shown that 10–15% of hyperandrogenic women with apparently normal cycles are anovulatory. In contrast, the finding of anovulation is very uncommon in normo-androgenic women with normal menses (Goodman et al. 2015). On the contrary, in women reporting oligomenorrhea, incidental ovulatory cycles might be recorded in up to 15% of cases (Burgers et al. 2010). Alternatively one might use the number of menstrual cycles per year to define oligomenorrhea. The Rotterdam consensus does suggest that if this number is less than eight, chronic anovulation should be suspected (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group 2004). Amenorrhea is arbitrarily defined as a menstrual cycle interval exceeding 188 days or being longer than half a year. Whenever irregular or absent menstrual cycles occur, a diagnosis of PCOS should be considered because approximately 85–90% of women with oligomenorrhea and 30–40% of women with amenorrhea will have PCOS (Neven et al. 2018).

Irregular cycles and ovulatory dysfunction are also a normal component of the pubertal and menopausal transitions, and defining cycle abnormalities at these life stages remains challenging. Indeed, the greatest controversy in this diagnostic criteria is during the pubertal transition. Irregular menstrual, and therefore anovulatory, cycles are common during the first year post menarche. Intermenstrual cycle intervals exceeding 90 days are mostly anovulatory in girls being between 1 and 3 years post menarche. Overall, irregular cycles (>35 or <21 days) that continue for more than 3 years post-menarche are likely to have oligo- or anovulation. With increasing gynecologic age, fewer females experience cycles exceeding 45 days (Teede et al. 2018).

Measurement of serum progesterone during the midluteal phase (days 21 to 22) is the best way to assess ovulation. Alternatives to a single progesterone measurement such as basal body temperature charts, urinary luteinizing hormone kits, or timed endometrial biopsies may be used, but they do not give sufficient information about the luteal phase, are elaborately costly, and should therefore not be used as first-line assessments tools (Legro et al. 2013).

## Hyperandrogenism

Hyperandrogenism is a key diagnostic feature of PCOS affecting between 60% and 100% with the condition with both clinical (hirsutism, alopecia, and acne) and biochemical hyperandrogenism. Both features of hyperandrogenism are challenging to assess and vary by methods of assessment, ethnicity, and confounding factors including excess weight and life stage. Methods for directly assessing total circulating testosterone levels (e.g., direct radioimmunoassays or chemiluminescence

immunoassays) are of insufficient precision, sensitivity, and specificity to be used for the accurate assessment of total testosterone levels in women and female adolescents, including those with PCOS. There are also currently no reliable direct assays for total or free testosterone. However, laboratories can provide calculated bioavailable testosterone, calculated free testosterone, or free androgen index (FAI = 100 × (total testosterone/sex hormone-binding globulin (SHBG))). Androstenedione and dehydroepiandrostenedione sulfate (DHEAS) have only a limited role and can increase the probability of detecting hyperandrogenemia, yet they are arguably more useful in exclusion of other causes of hyperandrogenism. DHEAS is predominantly an adrenal androgen, and mild elevation may be seen in conjunction with PCOS. Significant elevations of any androgen and/or virilization require investigation for possible androgen secreting adrenal or ovarian tumors. Androstenedione is elevated in 21-hydroxylase-deficient nonclassical congenital adrenal hyperplasia (Teede et al. 2018). PCOS is a diagnosis of exclusion. Hence, non-classic congenital adrenal hyperplasia, Cushing's syndrome, and androgen secreting tumors need to be excluded.

Signs and symptoms of severe androgen excess can result in virilization (e.g., male pattern balding, severe hirsutism, and clitoromegaly). Virilization is rare. Clinical evidence of mild to moderate androgen excess is more common including hirsutism, acne, and androgen-related alopecia. The interrelationship of these clinical features remains unclear, varies by ethnicity, and requires clinician training, vigilance, and skill to assess. These features impact considerably on quality of life in women with PCOS, and treatment burden including cosmetic therapies can be significant (Teede et al. 2018). When evaluating symptoms of hyperandrogenism, hirsutism should be assessed using the modified Ferriman-Gallwey score (mFG), assessing the existence and growth of terminal pigmented and medullated hair in nine masculine body areas. Each area is scored from 0 (no terminal hair) to 4 (terminal hair consistent with a well-developed male individual). A level exceeding 4–6 indicates hirsutism. The prevalence of hirsutism is the same across ethnicities, yet the mFG cutoff scores for defining hirsutism and the severity of hirsutism vary by ethnicity (Teede et al. 2018). Alopecia can be assessed using the Ludwig visual score. For acne, no universally accepted visual assessment is available (Neven et al. 2018).

## PCOM

Polycystic ovarian morphology (PCOM) was incorporated into the diagnosis of PCOS in 2003 in the Rotterdam criteria, as a common feature associated with clinical and endocrine features of the condition (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group 2004). This introduced arguably milder phenotypes into PCOS with limited data on natural history, prompting calls for phenotype identification and more research (Goodman et al. 2015). The definition of PCOM in the Rotterdam criteria is 12 or more follicles measuring 2–9 mm throughout the entire ovary or an ovarian volume $\geq$10 mL. This was based on a single report on

sensitivity and specificity in PCOS compared to controls (Balen et al. 2003). Factors that mandate revision of this diagnostic criteria include advances in ultrasound technology with greater resolution, variable operator skill level, lack of standard reporting, skill-defined cutoffs between normal ovaries and PCOM, the impact of the chosen approach (e.g., transvaginal vs. transabdominal), body habits, and age (Teede et al. 2018). Using newer ultrasound technology to count follicles, a substantially higher cutoff for PCOM than 12 follicles is required to distinguish between women with PCOS and healthy women from the general population (Lujan et al. 2013). Using the transvaginal approach, ultrasound transducers with a frequency bandwidth that includes 8 MHz, the threshold for PCOM should be on either ovary, a follicle number per ovary of $\geq$20 and/or an ovarian volume $\geq$10 ml, ensuring no corpora lutea, cysts, or dominant follicles are present. When using older equipment with transducer frequencies less than 8 MHz, the threshold for PCOM could be an ovarian volume $\geq$10 ml on either ovary (Teede et al. 2018).

In adolescents PCOM can also be detected without any of the accompanying features of PCOS, making it a common normal finding in these youngsters. Due to the high incidence of PCOM and its non-specificity in those with a gynecological age of less than 8 years post menarche, ultrasound is not recommended at this life stage for the purposes of diagnosis (Neven et al. 2018).

Women with PCOM have generally higher serum concentrations of anti-Mullerian hormone (AMH) and higher levels of AMH are associated with anovulation and hyperandrogenism (Mulders et al. 2004). Current research is evaluating whether serum AMH can replace ultrasound in the diagnosis of PCOM but is also hampered by poorly defined patient and control populations, variable quality between commercially available assays, and no international agreed standards (Victoria et al. 2019).

## Prevalence of Phenotypes

The Rotterdam criteria for PCOS recognize four different phenotypes (Table 1). A large meta-analysis including 41 studies reported on the prevalence of the 4 different phenotypes in referral versus unselected populations. Phenotype A was identified in up to 50% in patients referred to a hospital versus being present in only 19% in unselected populations. Similarly, phenotype B is 13% as prevalent in referred populations, whereas it is seen in up to 25% in unselected population-based samples. Phenotype C is present in about 14% of women referred to clinics versus 34% in unselected populations. Finally phenotype D is found in up to 17% of women attending clinics for PCOS, whereas a nearly similar (19%) number is found in unselected populations. Differences between referral and unselected populations were statistically significant for phenotypes A, B, and C. Moreover, it was noted that referred PCOS subjects had a greater mean body mass index (BMI) than local controls. This latter difference in BMI was not observed when unselected PCOS patients were compared to healthy controls. Hence, it seems to matter whether a woman is seeking medical assistance for her PCOS (Lizneva et al. 2016). There is

**Table 1** Phenotypes of PCOS according to the Rotterdam criteria

| | Diagnostic features of PCOS | | |
|---|---|---|---|
| | Oligo or amenorrhea | Clinical and/or biochemical hyperandrogenism | PCOM |
| Phenotype A | Present | Present | Present |
| Phenotype B | Present | Present | Absent |
| Phenotype C | Absent | Present | Present |
| Phenotype D | Present | Absent | Present |

*PCOS* polycystic ovary syndrome, *PCOM* polycystic ovarian morphology

still some controversy about whether or not the phenotypes A, B, and C are more often associated with metabolic derangements such as insulin resistance and obesity and dyslipidemia (Neven et al. 2018).

It should be noted that these three criteria for diagnosis of PCOS are subject to changes over time naturally occurring with increasing age and therefore impacting on the phenotype and presenting challenges in diagnosis (Brown et al. 2011). Overall it is acknowledged that there is inadequate evidence of the natural history of PCOS, and the concept of whether PCOS resolves and/or persists remains unclear pending better longitudinal studies. Postmenopausal phenotypes of PCOS are poorly defined, with limited longitudinal natural history studies. Uncertainty in assessment and diagnosis at this life stage leads to confusion for health professionals and women on long-term health risks and screening recommendations (Teede et al. 2018). However, postmenopausal persistence of PCOS could be considered likely with continuing evidence of hyperandrogenism after menopause. Similarly, a diagnosis of PCOS postmenopausal could be considered if there is a past diagnosis of PCOS, a long-term history of irregular menstrual cycles and hyperandrogenism and/or PCOM, during the reproductive years (Teede et al. 2018). Interestingly, women with PCOS generally enter menopause later in life compared to those who are not suffering from the syndrome. This is mainly due to a selective enrichment of menopause postponing genetic variants in women with PCOS (Day et al. 2015).

## Clinical Presentation

### Reproductive Features

PCOS is the most common cause of medically treatable infertility, and it accounts for up to 70% of cases of anovulatory infertility (Brassard et al. 2008). In a similar large study from Australia, anovulatory infertility was noted by 72% in women reporting to have been diagnosed with PCOS compared to an incidence of only 16% in those not reporting PCOS. Infertility was 15-fold higher in women reporting PCOS and was independent of BMI. In those women reporting infertility, there was greater use of fertility hormone treatment in women with PCOS although the incidence of ART use was similar in women with and without PCOS. Notably, the women with PCOS had a similar number of children as those without PCOS (Joham et al. 2015).

Women with PCOS had a four times increased risk of developing gestational diabetes compared with the reference group of pregnant women without PCOS. Moreover, the children born from mothers with PCOS were again nearly four times more often small for gestational age (de Wilde et al. 2017). In a subgroup analysis, maternal complications were statistically significantly more often present in hyperandrogenic PCOS women compared with those without hyperandrogenemia (de Wilde et al. 2017). In another study from the same group of investigators, a prediction model was designed to predict the chance of developing gestational diabetes in women with PCOS. First-degree relatives with T2DM, serum levels of fasting glucose, fasting insulin, androstenedione, and sex hormone-binding globulin before conception were identified as predictors (de Wilde et al. 2014). Primary disease characteristics of PCOS, chiefly hyperandrogenism and impaired glucose metabolism, seem to predict suboptimal obstetric and neonatal outcomes. According to these authors, increased surveillance during pregnancy in women with PCOS should focus on these clinical features, and this might help to mitigate obstetrical and neonatal risk (Christ et al. 2019).

A recent large meta-analysis examined the incidence of gynecological cancers in younger women with PCOS compared with controls of similar age. Current data suggest that women of all ages with PCOS are at an increased risk of endometrial cancer due to unopposed estrogen exposure due to their anovulatory status. In contrast the risk of ovarian and breast cancer was not significantly increased overall (Barry et al. 2014). It should however be noted that most studies addressing the risk of endometrial cancer did not take into account obesity, infertility, T2DM, and metabolic syndrome, all proven risk factors for endometrial cancer. In those studies where BMI was considered, associations with PCOS and endometrial cancer are less consistent (Harris and Terry 2016).

Because the menstrual cycle length shortens with increasing age in normal women in those suffering from PCOS, a similar shortening is noticed over time rendering a substantial number of these women eumenorrheic. Since menopause is also occurring later on in life in women with PCOS, regular ovulatory cycles are more frequent toward the end of their reproductive life span (Brown et al. 2011; Elting et al. 2003).

## Psychosocial Features

Several meta-analyses reported up to four times increased depressive symptom scores in women suffering from PCOS compared to healthy controls which persisted in BMI-matched studies. Although some studies reported increased scores that might not have been clinically significant, others showed increased moderate to severe depressive symptoms with a prevalence of depression of up to nearly 40% in women with PCOS opposed to an incidence of only around 15% in controls. Again these increased scores were independent of obesity and seen in both clinic and community recruits (Veltman-Verhulst et al. 2012; Dokras et al. 2011; Barry et al. 2011; Cooney et al. 2017).

Similarly, anxiety symptoms are also increased in women with PCOS. Several meta-analyses reported higher anxiety scores in PCOS compared to controls (Veltman-Verhulst et al. 2012; Barry et al. 2011). Another four studies reported a sevenfold increase in abnormal anxiety scores in PCOS (Dokras et al. 2012). Again there was considerable heterogeneity between studies in all meta-analyses. A recent rigorous meta-analysis showed increased moderate/severe anxiety symptoms in PCOS with a prevalence of 42% in women with PCOS compared to only 9% in controls (Cooney et al. 2017). A large population-based study of 24,385 women with PCOS matched for sex, age, and country of birth to 10 controls showed increased anxiety disorder (Cesta et al. 2016). A large hospital database showed anxiety in PCOS at 14%, compared to 6% of those without a diagnosis of PCOS (Hart and Doherty 2015). Collectively, these studies indicate increased anxiety symptoms and anxiety disorders in women with PCOS, across diverse ethnic groups. Interestingly, a large study in a Swedish cohort of twins revealed common genetic factors between neuroticism, PCOS, and major depressive disorder. That study concludes that neuroticism shares approximately half of the genetic and environmental components behind the phenotypic correlation between PCOS and major depression disorder and thus provides some etiological evidence behind the comorbidity between PCOS and depression (Cesta et al. 2017). In the context of PCOS, identification of psychological features and mental health disorders is crucial to address gaps in care identified by affected women, to improve well-being and quality of life, facilitate appropriate referral and care, and optimize engagement with lifestyle and preventive strategies. However, overdiagnosis of depression and anxiety should also be avoided (Teede et al. 2018).

In a recent meta-analysis, significant small effect sizes were found on sexual function subscales such as arousal, lubrication, satisfaction, and orgasm, indicating impaired sexual function in women with PCOS. Larger effect sizes were seen on sexual function and feelings of sexual attractiveness. Satisfaction with sex life was impaired as well; however, sexual satisfaction was rated equally important in women with PCOS and controls. Physical PCOS symptoms such as hirsutism, obesity, menstrual irregularity, and infertility may cause loss of feminine identity and a feeling of being unattractive which may impact on sexuality (Pastoor et al. 2018).

Surveys in PCOS show mixed results across the different disorders, but overall a recent systematic review and meta-analysis suggest an increased prevalence of eating disorders and disordered eating in women with PCOS. Women with PCOS also have more identified risk factors for eating disorders such as obesity, depression, anxiety, self-esteem, and poor body image (Lee et al. 2018).

## Metabolic Features

Obesity is neither necessary nor sufficient for the PCOS phenotype, and the association of PCOS with obesity is not universal with national, cultural, and ethnic differences. However, the incidence of obesity in women with PCOS is increased

compared to women without PCOS. Particularly visceral adiposity is the common entity in obese and nonobese women with PCOS, which amplifies and worsens all metabolic and reproductive outcomes. Hence, obesity increases insulin resistance and the resulting hyperinsulinemia, which in turn increases adipogenesis and decreases lipolysis. Obesity also sensitizes thecal cells to LH stimulation and thereby causes functional ovarian hyperandrogenism. Obesity also impacts on inflammatory adipokines which, in turn, increase insulin resistance and adipogenesis (Glueck and Goldenberg 2019).

PCOS is associated with insulin resistance and hyperinsulinemia (Dumesic et al. 2015). A recent meta-analysis of clamp assessments of insulin action in PCOS found a decrease in insulin sensitivity of nearly 30% in women with PCOS compared with controls. This decrease in insulin sensitivity was independent of BMI, age, or diagnostic criteria. BMI exacerbated insulin resistance by 15% in women with PCOS and had a greater impact on insulin resistance in PCOS than in controls (Cassar et al. 2016). PCOS is associated with impaired glucose tolerance in up to 30% and T2DM in up to 10% of women with PCOS (Legro et al. 1999). When followed up over 10 years, the age-standardized prevalence of diabetes was nearly 40% in women with PCOS compared to only 5% in controls of similar age (Gambineri et al. 2012). Different phenotypes show different levels of insulin resistance being the most prevalent in the full-blown clinical picture (phenotype A), whereas phenotype C is not associated with insulin resistance (Panidis et al. 2012). It is estimated that about 2% of women with PCOS progress directly from baseline normoglycemia to T2DM. Moreover, every year about 16% progress from impaired glucose tolerance to T2DM. The prevalence of T2DM in PCOS continues to increase during the late reproductive years (Gambineri et al. 2012; Norman et al. 2001; Hudecova et al. 2011). Glycemic status should be assessed (using an oral glucose tolerance test [OGTT], fasting plasma glucose, or HbA1c) at baseline in all women with PCOS and should be repeated every 1 to 3 years depending on other individual risk factors for diabetes present. 5 A 75-g OGTT is recommended for women with additional risk factors and preconception and during pregnancy (Teede et al. 2018).

Nonalcoholic fatty liver disease seems to be as prevalent as 50% in patients with PCOS compared to controls. Women with PCOS had significantly higher values for waist circumference, lipid accumulation products, insulin and HOMA-IR, total cholesterol, and triglycerides than controls (Macut et al. 2016).

Women with PCOS are generally more overweight and obese compared to their age-matched counterparts without the syndrome. Because they also suffer from insulin resistance and the resulting hyperinsulinemia, dyslipidemia, and hypertension, they also are much more often affected by the so-called metabolic syndrome (Azziz et al. 2016; Dumesic et al. 2015). Also, metabolic syndrome, hypertension, and dyslipidemia are all reported to be significantly increased in first-degree relatives of women diagnosed with PCOS. It might therefore be that these families are already a priori more at risk and more susceptible for metabolic syndrome (Yilmaz et al. 2018; Laven 2018).

Cardiovascular disease (CVD) remains one of the leading causes of death in women, and any condition further increasing CVD risk will have significant public health impact. CVD primarily affects postmenopausal women in the later decades of life; however, CVD development and risk factors are present in early adulthood. A meta-analysis found no statistical difference between PCOS and non-PCOS groups in terms of myocardial infarction, stroke, CVD-related death, and coronary artery/heart disease (Heida et al. 2016; de Groot et al. 2011). Some age classes where apparently more at risk than others in some studies. However, when all age groups were combined, there was no difference in risk between women with and without PCOS, for either myocardial infarction or angina, regardless of where the control population was sourced (Heida et al. 2016). Given the methodological and reporting limitations and small sample sizes of these observational studies, all findings should be interpreted with caution. Furthermore the relatively young age of women included in most studies limits the interpretation of the available data (Teede et al. 2018). One large population-based Dutch study did assess the impact of hyperandrogenemia, assessed around their perimenopausal transition, on CVD outcome in women currently aged between 70 and 80 years of age. This prospective study was not able to show any relationship between androgens and CVD risk. Moreover, in a subpopulation with PCOS, they recorded a similar incidence of CVD, stroke, and coronary heart disease compared to age and BMI-matched women without PCOS (Meun et al. 2018). A second large hospital-based Danish population study did report an increased event rate of CVD including hypertension and dyslipidemia which was higher in women with PCOS compared to controls. They included hospital-referred PCOS patients and compared them to population-based controls which might have caused ascertainment bias. Also their definition of CVD was very broad including both prevalent and incident events (Glintborg et al. 2018). The only prospectively designed study with sufficiently long follow-up was published by a Swedish group. That study reported an increased incidence of neither myocardial infarction nor stroke or ischemic heart disease in women with PCOS compared to age-matched controls without PCOS (Schmidt et al. 2011).

It is acknowledged that metabolic syndrome and CVD risk factors are clearly increased in PCOS and that cardiovascular health overall needs to be considered; however, given the limited current data on clinical events, overall CVD risk and optimal screening for additional risk factors remains highly controversial (Teede et al. 2018).

## Pathophysiology

PCOS is a complex multifactorial disease where genetic, endocrine, environmental, and behavioral factors are intertwined. The interplay between these mechanisms results in and perpetuates the clinical features of PCOS, including ovulatory dysfunction, hyperandrogenism, and PCOM, in addition to the associated mood disturbances, psychosexual dysfunction, and long-term morbidities (Azziz et al. 2016) (Fig. 1).

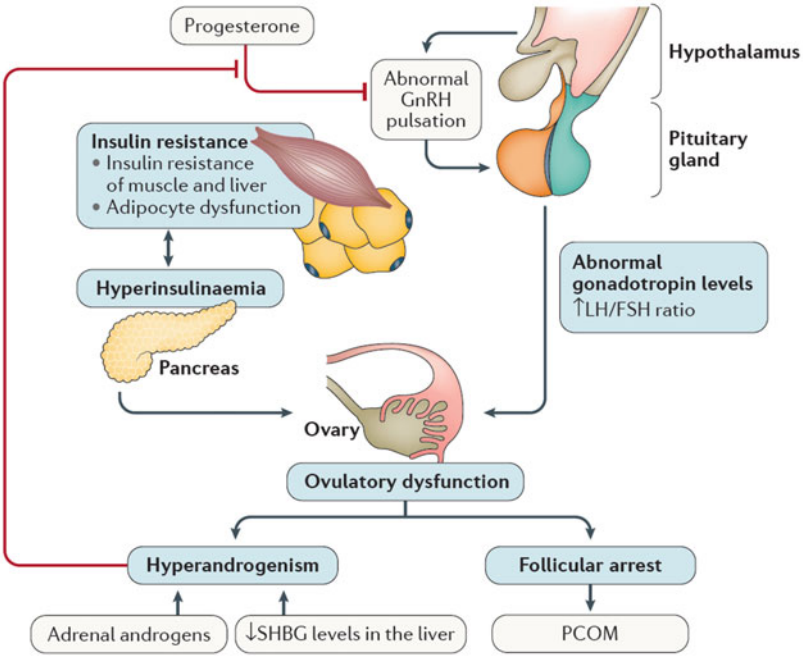


**Fig. 1 The pathophysiology of PCOS.** The pulsatile release of gonadotropin-releasing hormone (GnRH) from the hypothalamus is often disturbed in polycystic ovary syndrome (PCOS), leading to luteinizing hormone (LH) hypersecretion by the pituitary gland, which induces ovulary dysfunction and hyperandrogenism. This perturbed secretion of LH seems to arise early in puberty and is related to disturbed inhibition of GnRH secretion by progesterone. Although serum follicle-stimulating hormone (FSH) levels are generally normal, follicles seem to be more resistant to FSH in women with PCOS than in controls. This effect might be due to increased levels of intra-ovarian anti-Müllerian hormone (AMH). Notably, genetic and epigenetic variants contribute considerably to susceptibly for most of these alterations. Environmental factors contribute somewhat less, most by exacerbating insulin resistance and dysregulated gonadotropin secretion. PCOM, polycystic ovarian morphology; SHBG, sex hormone-binding globulin. Source: Azziz et al. (2016)

## Genetic Factors

Several hundreds of candidate genes have been studied; however, the majority of these genetic variants have not been replicated in sufficiently large case control studies. Genetic variants in the *fibrillin* gene, the androgen receptor, *FTO* gene, the insulin receptor, the *FSHR* gene, the *TNF alpha* gene, and some variants in the *IL-6* gene do confer a certain risk for PCOS and have been replicated in sufficiently large studies or meta-analyses (Azziz et al. 2016).

More recently, GWAS has identified up to 20 genetic variant genes involved in neuroendocrine, metabolic, and reproductive pathways. These studies also provided evidence for shared biologic pathways between PCOS and a number of metabolic disorders, menopause, depression, and male-pattern balding, a putative male phenotype (Day et al. 2015, 2018; Hayes et al. 2015; Chen et al. 2011). There is not much

of overlap between GWAS findings and most functional molecular studies. Most of the identified SNPs seem to play a role in a pathway responsible for trafficking and recycling of large protein transmembrane receptors (McAllister et al. 2015). Moreover, some promising SNPs involved in gonadotropin action have been identified which do not only constitute risk factors for PCOS but also seem to influence response to ovulation induction treatment (Valkenburg et al. 2015; Laven 2019).

Last but not least, evidence is accumulating that epigenetic mechanisms might as well play a role in the pathogenesis of PCOS either during fetal programming or in later life via factors as obesity and diet composition (Mykhalchenko et al. 2017).

## Endocrine Factors

Pathophysiology of PCOS as well as potential mechanisms underlying anovulation in PCOS are explained in Figures 1 and 2. In women with PCOS, there is an increased production of LH from the pituitary concomitant with a decrease in the secretion of follicle-stimulating hormone (FSH) leading to an increased LH/FSH ratio. The reason for this seems to be a perturbed gonadotropin-releasing hormone (GnRH) pulse generator in the hypothalamus. This increased LH pulsing is already obvious in young girls during their pubertal transition (Burt Solorzano et al. 2012). Moreover, neurokinin B receptor (NK3-R) antagonist specifically reduced LH pulse frequency and subsequently serum LH and testosterone concentrations, thus presenting NK3-R antagonism as a potential approach to treating the central neuroendocrine pathophysiology of PCOS (George et al. 2016). Interestingly, more recently AMH type II receptors were found on GnRH neurons in the midbrain in rodents as well as in humans. By administering AMH directly to these GnRH neurons in rodents, as well as in vitro and in vivo, they responded with an increase in LH

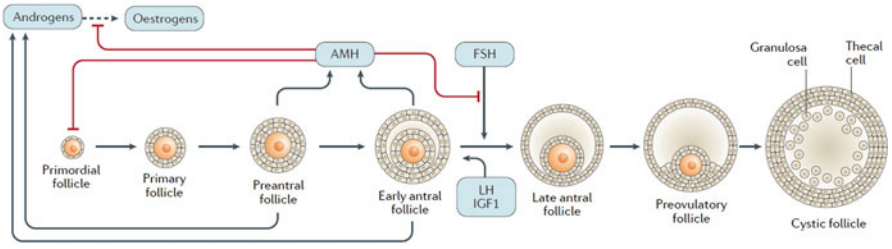


**Fig. 2** Anovulation in PCOS explained. **Ovarian follicular maturation arrest in PCOS.** Normal ovulation is the result of synchronized signalling between centrally released gonadotropins and factors produced in the developing follicle of the ovary. Anovulation in women with polycystic ovary syndrome (PCOS) is characterized by arrested follicle growth at the early antral stage. Hypersecretion of luteinizing hormone (LH) and insulin-like growth factor 1 (IGF1) lead to hyperandrogenism, which results in follicular maturation arrest93. In addition, high levels of anti-Müllerian hormone (AMH) in PCOS block follicle-stimulating hormone (FSH) action contributing to hyperandrogenism and inhibiting the recruitment of further primordial follicles. Dashed line indicates androgen to oestrogen conversion. (Source: Azziz et al. (2016))

release and a decrease in FSH release leading to an increased LH/FSH ratio. These findings raise the intriguing hypothesis that AMH-dependent regulation of GnRH release could be involved in the pathophysiology of fertility and could hold therapeutic potential for treating PCOS (Cimino et al. 2016). In a second study, the same group showed that excessive intrauterine exposure of offspring to AMH induced a neuroendocrine-driven androgen excess with perturbed GnRH pulsatility leading to follicular arrest. Treatment with a GnRH agonist did restore their neuroendocrine phenotype to a normal state (Tata et al. 2018).

Hyperinsulinemia might also contribute to the clinical picture since theca cells seem to be more sensitive to LH and insulin causing them to produce more androgens upon stimulation compared to theca cells of normal women. Moreover, insulin does inhibit the production of SHBG in the liver, thereby even further increasing the amount of free androgen serum levels (Azziz et al. 2016). Similarly, although women with PCOS can show little difference in fat distribution and possibly in overall BMI, strong evidence supports that adipocytes and adipocyte function are aberrant in PCOS, favoring insulin resistance and subclinical inflammation which in turn might contribute to the perturbed endocrine environment in women with PCOS (Azziz et al. 2016).

## Environmental and Behavioral Factors

Regardless of the specific diagnosis, patients with eating disorders (ED) have several features in common with women with PCOS. Both groups are at higher risk of depression and anxiety, body image disturbances, and significant detrimental effects on quality of life. The binge eating disorder (BED) is particularly relevant to PCOS, as it is independently associated with diabetes mellitus, obesity, and hypertension, and all comorbidities are also associated with PCOS (Dokras et al. 2012; Lee et al. 2018). Of note, women with PCOS often report that weight loss is more challenging for them than for women without PCOS. This may place them at risk for disordered eating behaviors, such as severe restricting, binge eating, and/or inappropriate compensatory behaviors. Therefore, both the potential effect of ED on treatment of PCOS and the possible increased risk of ED in those with PCOS drive the need to evaluate the precise prevalence of ED in women with PCOS (Lee et al. 2018). It is undeniably important to promote weight loss in women with PCOS given the impact on insulin sensitivity and reproductive function; however, the potential paradoxical harm in overemphasizing the value of weight loss cannot be dismissed (Lee et al. 2018).

Obstructive sleep apnea (OSA) is characterized by repetitive occlusions of the upper airway during sleep with futile ventilatory efforts, oxygen desaturations, sleep arousal, and the resumption of ventilation, fragmenting sleep and causing daytime sleepiness. Hence, OSA might affect quality of life, mood, and productivity. OSA appears more common in PCOS and in obesity, a common corollary of PCOS. In PCOS an increased prevalence has been reported which was not only explained by obesity (Mokhlesi et al. 2012). Hyperandrogenism may also contribute to OSA and

there are links to metabolic syndrome (Tasali et al. 2011). Although treatment studies in PCOS are very limited, successful treatment of OSA improves insulin sensitivity, decreases sympathetic output, and reduces diastolic blood pressure. The magnitude of these beneficial effects is modulated by the hours of CPAP use and the degree of obesity (Tasali et al. 2011).

## Treatment

### Reproductive Disorders

The ultimate goal in treating fertility disorders in PCOS is restoring normal mono-ovulation. Indeed many physicians do not discriminate between ovarian hyper-stimulation and ovulation induction both being different treatment protocols with different treatment goals (The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). There are several ways to achieve mono-ovulation: either one uses drugs that increase the endogenous levels of FSH or one might directly administer FSH to the patients. The first group consists of the antiestrogens or aromatase inhibitors. Antiestrogens, such as clomiphene citrate, decrease the negative feedback on the hypothalamus and pituitary leading to an increase in the release of endogenous FSH which in turn might induce ovulation. Aromatase inhibitors, such as letrozole, reduce the conversion of androgens into estrogens, thereby again reducing the negative feedback of estrogens on the hypothalamic pituitary axis and thereby increasing the endogenous FSH release from the pituitary. Several trials have compared letrozole with clomiphene citrate, and a recent network meta-analysis concluded that in normogonadotropic normo-estrogenic anovulatory women, letrozole is superior to clomiphene citrate. Compared with clomiphene alone, letrozole is the only treatment showing a significantly higher rate of ovulation, higher pregnancy rates, and higher live birth rates. Moreover, letrozole and the combination of clomiphene citrate with metformin were superior to clomiphene citrate alone in terms of ovulation and pregnancy rates. There was no difference between letrozole and clomiphene citrate for multiple pregnancy rate per patient and miscarriage rate per patient (Wang et al. 2017; Franik et al. 2018). The balance of benefits in terms of improved live births with letrozole and less hot flushes was considered to currently outweigh the adverse effects of relatively increased fatigue and dizziness, multiple pregnancy, and unconfirmed concerns about higher congenital anomalies (Teede et al. 2018; Franik et al. 2018). In most countries, letrozole can only be used off label in those instances one might consider to use clomiphene citrate alone in anovulatory PCOS women to improve ovulation and pregnancy rates. Similarly, metformin could be used alone in anovulatory women with PCOS to improve ovulation, pregnancy, and live birth rates, although women should be informed that there are more effective ovulation induction agents. Clomiphene citrate seems to be superior to metformin in anovulatory PCOS women in case these women have a BMI of over 30 kg/m$^2$ (Teede et al. 2018).

In case the first-line treatment is not successful or patients are resistant to the oral medication because they do not ovulate, gonadotropin therapy might be initiated. Again the goal here is induction of one dominant follicle. Gonadotrophin therapy is suitable for improving infertility in women with PCOS in specialist care, with close monitoring with ultrasound and strict criteria to cancel cycles in case of multiple follicle development (The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008). Gonadotropin therapy provides better per cycle and cumulative pregnancy and live birth rates compared with the use of oral antiestrogens and/or no therapy at all (Wang et al. 2017). An extra advantage is that there is no evidence of teratogenicity although the risk of multiple pregnancy is increased as is the cost of medication when compared to the oral agents (Teede et al. 2018). Another second-line treatment option is laparoscopic ovarian drilling, in order to reduce the number of follicles, an intervention that can lead to a singleton birth in women with PCOS. There is no convincing evidence of inferiority over other common ovulation induction agents. An extra advantage is that there is no need for monitoring and only a background risk of multiple pregnancy. However, it is important to note that laparoscopic ovarian drilling is an invasive surgical intervention. Moreover, there is a small risk of reduced ovarian reserve or loss of ovarian function afterward and an increased chance of adhesion formation (Lepine et al. 2017). A recent meta-analysis indicated that a unilateral procedure might be as effective as bilateral drilling (Abu Hashim et al. 2018).

In the absence of an absolute indication for IVF with or without ICSI, women with PCOS and anovulatory infertility could be offered IVF as third-line therapy where first- or second-line ovulation induction therapies have failed. IVF should be considered after failed ovulation induction treatment with high pregnancy rates per cycle, especially in younger women. Given the risks and the high costs that can be prohibitive for many patients, IVF should be considered third-line medical therapy. Indeed, the use of IVF is effective, and when elective single embryo transfer is used, multiple pregnancies can be minimized (Teede et al. 2018). It seems that in case a short protocol with a GnRH antagonist is used in combination with an agonist trigger, the chances for ovarian hyperstimulation syndrome are reduced. However, GnRH agonist triggers are associated with lower pregnancy rates, primarily in fresh embryo transfers, which can be overcome in frozen cycles. Similarly, in vitro maturation (IVM) of oocytes limits or omits ovarian stimulation prior to oocyte retrieval, with maturation of oocytes post-retrieval, avoiding OHSS risk (Teede et al. 2018).

Combined contraceptives, including oral contraceptive pills, are commonly prescribed for adults and adolescents with PCOS without wish to conceive to ameliorate the clinical symptoms and associated hormonal disturbances. The effects of COCPs on menstrual cycle, hirsutism, weight loss, waist/hip ratio, testosterone concentrations, lipid profile, and blood sugar levels are variably reported and depend on the type of COCP used, duration of use, severity of presentation/phenotype, and adherence to the regimen, among other factors. Different combinations of COCPs are available with heterogeneous estrogen and progestin preparations with varying pharmacological and clinical properties. Thus, the efficacy and consequences of

COCPs in PCOS may vary. Some preparations also comprise natural estrogen instead of synthetic ethinylestradiol with benefits and contraindications considered similar (Teede et al. 2018). The use of antiandrogens in combination with COCP should only be considered in women with PCOS to treat hirsutism and androgen-related alopecia exclusively in case COCP and cosmetic therapy have failed to adequately improve symptoms. Where COCPs are contraindicated or poorly tolerated, in the presence of other effective forms of contraception, antiandrogens could be considered to treat hirsutism and androgen-related alopecia (Azziz et al. 2016; Teede et al. 2018).

## Metabolic Disorders

Given the gaps in evidence in some areas in PCOS, the relevant literature on metformin in other populations was reviewed to inform recommendations. Metformin works by decreasing gluconeogenesis and lipogenesis and enhancing glucose uptake in the liver, skeletal muscle, adipose tissue, and ovaries (Teede et al. 2018). It is known in other populations to prevent weight gain and appears to assist with weight loss, to prevent and manage T2DM and gestational diabetes (GDM), and to reduce microvascular and cardiovascular disease (Naderpoor et al. 2015). Side effects are not uncommon, yet these are primarily gastrointestinal and appear mild and self-limiting (Naderpoor et al. 2015). Concerns on vitamin B12 deficiency with longer-term metformin use have also emerged; however, more research is needed. Data from other populations suggests that side effects can be minimized with lower metformin starting dose, extended release preparations and/or administration with food (Teede et al. 2018).

The most recent literature would suggest that inositol could represent an important therapeutic strategy for the improvement of metabolic aspects of PCOS (Gateva et al. 2018). Similarly, inositol might also improve reproductive outcomes. Moreover, inositol seems effective in preventing and treating GDM although larger cohort studies are needed to better clarify these results (Gateva et al. 2018).

Lifestyle intervention, preferably multicomponent including diet, exercise, and behavioral strategies, should be recommended in overweight or obese women with PCOS to effectively reduce weight, central obesity, and insulin resistance (Moran et al. 2011).

A recent meta-analysis including 29 studies revealed that in severely obese patients submitted to bariatric surgery, obesity-associated gonadal dysfunction was very prevalent. PCOS was present in nearly 40% of cases. After bariatric surgery, resolution of PCOS was found in nearly all cases of affected women. SHBG concentrations increased after bariatric surgery in women, whereas serum estradiol concentrations decreased in women with PCOS. Similarly, total testosterone serum levels decreased in women. The latter was accompanied by resolution of hirsutism in nearly half of the cases and a reduction in the incidence of menstrual dysfunction in nearly all cases of women showing these symptoms before surgery (Escobar-Morreale et al. 2017).

## Psychosocial Disorders

Although there is no compelling evidence that behavioral modifications might work in women with PCOS, they do so however in other high cardiometabolic risk populations. In those studies behavioral change strategies and/or behavioral/cognitive interventions in combination with diet and exercise improved weight loss and were more effective than diet and/or physical activity alone. Emphasis on self-management components enhances weight loss and healthy lifestyle behavior change and is incorporated into advice on lifestyle interventions for the general population. Skill levels among health professionals may vary, presenting implementation challenges (Moran et al. 2011; Wing et al. 2008). The effectiveness of lifestyle programs seems to be improved when incorporating behavioral strategies such as goal setting, self-monitoring, stimulus control, problem-solving, assertiveness training, slower eating, reinforcing changes, and relapse prevention, to optimize weight management, healthy lifestyle, and emotional well-being (Neven et al. 2018).

Although extensive information on diet types in women with PCOS is lacking, there is no benefit of any one diet type and that hormone levels including insulin do not predict responses. There is currently no evidence that modifying dietary macronutrient composition offers additional benefits over conventional dietary approaches for weight loss, and further research is needed (Moran et al. 2009).

Exercise should be encouraged and advised in PCOS. It was considered that exercise interventions and physical activity do not require clinical centers, expensive gyms, and fitness centers. They can be delivered in community centers, sporting grounds/facilities, in groups, and with minimal equipment. Low-cost e-health (electronic health) and m-health (mobile health) options may also be used (Teede et al. 2018; Moran et al. 2009).

Detection of negative body image provides the opportunity to address both psychological aspects such as self-esteem and self-acceptance and working on the physical aspects of the condition such as hirsutism, overweight, and acne, if appropriate. Evidence specific to PCOS models of care is limited; however, existing evidence suggests integrated multidisciplinary services, support groups, and nurse-led education can address identified gaps, increase understanding of PCOS, and improve lifestyle change (Neven et al. 2018). Needs differ by individual and life stage. Cultural influences need to be considered in PCOS in the context of both care and information needs. Culturally appropriate care involves more than linguistic considerations (Teede et al. 2018).

Some of the PCOS-related treatments including lifestyle modification, OCPs, laser treatment, and insulin sensitizers have shown favorable effects on depression or anxiety symptoms. Generally, these interventions are also well tolerated with a favorable side effect profile and thus can be continued in women diagnosed with depression or anxiety disorder. In addition, women with a clinically confirmed diagnosis of depression or anxiety should be treated based on standard guidelines. Future studies should focus on understanding the mechanisms that lead to the increased risk of depression and anxiety in women with PCOS and the best interventions in this population which is already at risk for several comorbidities (Cooney and Dokras 2017).

## Conclusions

PCOS is a complex disease where genetic, endocrine, environmental, and behavioral factors are intertwined with each other giving rise to a heterogeneous phenotype with reproductive, metabolic, and psychological characteristics that affect women's health and quality of life across the life course. Physicians should be aware of the clinical features and risks for women with PCOS and screen and manage them accordingly. Clinicians should focus on lifestyle adjustments as the first-line management to improve reproductive, metabolic, cardiovascular, and psychosocial outcomes focusing on weight management and physical exercise as well as on cognitive behavioral interventions. In addition, pharmacological therapy in the form of COCPs and metformin may be useful. Similarly, for anovulatory infertility, lifestyle modification is also recommended as first-line treatment. If this is unsuccessful, ovulation induction using letrozole is the first-line medical management, whereas clomiphene citrate and metformin may have an additive effect. Gonadotrophins and laparoscopic drilling are second-line treatment options, whereas IVF constitutes the third-line therapy option only indicated when other fertility treatments have failed.

The latest international evidence-based guideline for PCOS details these treatments along with providing translation resources for health professionals or women with PCOS. Together these are designed to provide a valuable resource aiding clinicians in optimal assessment and management of women with PCOS.

## Cross-References


- ▶ Endocrinology of Maternal-Placental Axis
- ▶ Hormonal Contraception
- ▶ Hormonal Treatments in the Infertile Women
- ▶ The "Great Obstetrical Syndromes"
- ▶ The Hypothalamus-Pituitary-Ovary Axis
- ▶ The Menstrual Cycle and Related Disorders
- ▶ The Menstrual Disorders Related to Systemic Diseases


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