

Understanding Polycystic Ovary Syndrome:

Symptoms, Diagnosis, Treatment and Future Directions

Abstract

Polycystic ovary syndrome (PCOS) is the commonest metabolic and endocrine disorder that affects women of reproductive age. It is characterised by irregular menstruation, hyperandrogenism and polycystic ovarian morphology.

While significant progress has been made in understanding PCOS, several research questions remain. For instance, there is a need for further investigation into the aetiology of PCOS, including the role of genetic and environmental factors, to aid in earlier diagnosis and treatment. Additionally, while some therapies have been effective in managing the symptoms of PCOS, their long-term efficacy and safety remain uncertain. There is a need to better understand the long-term health consequences of PCOS, particularly regarding cardiovascular disease and cancer risk.

Early diagnosis, lifestyle modifications, and appropriate medical interventions can help to reduce the risk of complications and improve the overall health outcomes of women with PCOS. Looking forward, there is a need for a multidisciplinary approach to studying PCOS, including collaborations between researchers, healthcare providers, and patient advocacy groups. This may involve developing new tools and technologies for diagnosis and treatment, as well as exploring novel interventions and therapies.

There is a growing recognition of the importance of PCOS as a major health issue affecting millions of women worldwide, and continued research efforts will be critical for improving diagnosis, treatment, and long-term outcomes for those affected by the condition.

Key words

Polycystic ovary syndrome; metabolic syndrome, women of reproductive age, infertility

Introduction

Polycystic ovary syndrome (PCOS) is a common metabolic and endocrine disorder that affects

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women of reproductive age. It is characterised by irregular menstruation, hyperandrogenism and polycystic ovarian morphology¹. PCOS is prevalent, affecting approximately 5-20% of women, depending on the definition used². It is the most common endocrine disorder in females of reproductive age.

The syndrome is a major cause of menstrual abnormalities, hirsutism, and female anovulatory infertility³. In addition, PCOS is associated with various health conditions, including insulin resistance, metabolic syndrome, increased risk of cardiovascular disease, pregnancy-related complications, and psychological problems⁴. Although PCOS has no cure, management typically involves lifestyle changes, medications, and on occasion surgical interventions, tailored to an individual's symptoms, age and fertility goals, with an aim to reduce symptom burden and risk factors.

Despite ongoing research, there remain significant challenges in the diagnosis and management of PCOS. The pathophysiology of PCOS is complex and not fully understood, leading to a lack of consensus and awareness regarding diagnosis and treatment⁵. Women with PCOS often report delays in diagnosis⁶ and dissatisfaction with treatment options⁷. This paper presents a comprehensive overview the current state of progress in PCOS, as well as highlighting the challenges faced in its diagnosis and management, and identifying potential future directions for research.

Diagnostic criteria

The diagnostic criteria for PCOS have long been a topic of controversy and discussion. Currently, there is no single diagnostic test available for PCOS. Instead, the diagnosis is based on the presence of three main characteristics: irregular menstruation (oligomenorrhoea), hyperandrogenism (either clinical or biochemical), and polycystic ovarian morphology (PCOM) observed on ultrasound⁸. These three factors are collectively referred to as the Rotterdam criteria, and the presence of two out of three is required to diagnose PCOS, with the exclusion of other diseases such as thyroid

disease, Cushing's syndrome and androgen-secreting tumours⁹. PCOS is classified into four subtypes based on the presence or absence of the three key diagnostic criteria, and different subtypes may have an increased risk of specific complications, such as metabolic dysfunction^{8,10}. Biochemical hyperandrogenism is characterised by an increase in serum total and free testosterone and androstenedione and increased free androgen index (FAI).

Rotterdam Criteria for diagnosis of PCOS

- irregular menstruation (oligomenorrhoea),
- hyperandrogenism (either clinical or biochemical), and
- polycystic ovarian morphology (PCOM) observed on ultrasound

Variations in diagnostic features based on age and ethnicity present further challenges for diagnosis. Normal physiological changes during puberty, such as irregular menstrual cycles and multifollicular ovaries, can mimic PCOS symptoms, leading to an increased risk of both underdiagnosis and overdiagnosis of the syndrome^{6,8}. Hyperandrogenism can be defined either biochemically or clinically. However, when evaluating the clinical features of androgen excess, such as hirsutism, acne, or alopecia, significant variations may arise depending on the patient's ethnicity, and examination may be limited by self-treatment of hirsutism. Ultrasound morphology also poses a challenge for diagnosing PCOS due to variations in follicle count cut-offs and advancements and availability of technology⁸.

Aetiology

The pathophysiology and aetiology of PCOS involves a complex interplay of genetic and environmental factors that disrupt the functioning of the hypothalamus-pituitary-ovarian axis, leading to hyperandrogenism.

Insulin resistance is another major component, caused in part by the accumulation of adipose tissue resulting from hyperandrogenism and oxidative stress¹¹. The multifactorial nature of PCOS results in a constellation of effects that include metabolic, reproductive, and psychological impairments⁸. In addition, there is a correlation between increased body mass index (BMI) and the prevalence of PCOS. A study conducted by Teede et al. in 2013 showed that the prevalence of PCOS in women with BMI <25 kg/m² was 4.3%, compared to 14% in women with BMI >30 kg/m²¹².

Recent research has identified several genes implicated in the aetiology of PCOS, making it a polygenic and multifactorial syndrome. Genome-wide association studies have identified 19 risk gene loci for PCOS located in the neuroendocrine, metabolic, and reproductive pathways¹³. The pathophysiology of PCOS involves multiple genetic pathways, making it currently unfeasible to develop a single genetic diagnostic test. While the exact mechanisms by which variants in the genes confer risk to PCOS remain to be determined, uncovering candidate genes and cellular pathways involved in PCOS will increase understanding of the pathophysiology of PCOS and hopefully lead to more targeted management options¹⁴.

Risk associated with PCOS

PCOS is associated with various complications and health risks. For instance, it is linked to a higher risk of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), pregnancy-related complications, psychological disorders, and endometrial cancer¹. PCOS is considered a metabolic syndrome, and many of these associations are thought to be related to PCOS-induced insulin resistance.

Cardiovascular disease risk

The increased risk of CVD is thought to be due to the metabolic abnormalities associated with PCOS, such as insulin resistance, impaired glucose tolerance, obesity, and dyslipidaemia¹. These metabolic abnormalities also increase the risk of developing T2DM and hypertension, which are themselves risk factors for CVD. A meta-

analysis conducted in 2012 showed that the risk of obesity was four times higher in women with PCOS when compared to controls¹⁵. Additionally, the pattern of obesity in women with PCOS tends to fit the hyperandrogenic phenotype, with preferential abdominal fat deposition, further increasing the risk of CVD¹⁶.

Reproductive and obstetric risks

PCOS is linked to various reproductive and obstetric risks, ranging from fertility impairment to pregnancy-related complications¹⁷. The latter includes an increased risk of pre-eclampsia, gestational diabetes mellitus, pregnancy-induced hypertension, and miscarriage¹⁸. Although the mechanisms underlying these risks are not completely understood, it is thought that the increased risks are related to the endocrine and metabolic dysregulation in women with PCOS, such as hyperandrogenism and elevated BMI¹⁷. Given these risks, it is important to provide prenatal counselling for women with PCOS, as well as enhanced antenatal care, such as regular monitoring for pregnancy-related hypertension and gestational diabetes mellitus.

Risk of malignancy

PCOS is associated with an increased risk of endometrial cancer, which may be further exacerbated by comorbidities such as obesity, infertility, and type 2 diabetes mellitus¹⁹. Perimenopausal women with PCOS have an approximately four times increased risk of endometrial cancer²⁰, however the absolute risk of endometrial cancer remains relatively low⁴. The exact pathophysiology of this association is not fully understood, but it is thought to be related to the anovulatory cycles that occur in women with PCOS, leading to continuous exposure of the endometrial lining to oestrogen¹⁷. It is important for healthcare professionals to be aware of this increased risk, and adopt a low threshold for investigation of endometrial cancer in women with PCOS who present with risk factors such as prolonged amenorrhoea, abnormal vaginal bleeding or increased BMI. Investigations in such women include transvaginal ultrasound plus or minus endometrial biopsy. However, routine ultrasound screening for endometrial thickness

in women with PCOS is currently not recommended⁴.

Psychological impacts

The psychological effects of PCOS represent an important yet under-researched aspect of this condition. Living with PCOS has been shown to have a significant impact on mood and psychological well-being, potentially due to factors such as body image and the long-term health implications of the condition²¹. Evidence suggests that women with PCOS are at a higher risk of depression, anxiety, negative body image, and psychosexual dysfunction²¹. It is crucial to consider how these negative psychological factors may affect the patient's ability to maintain the lifestyle changes that are essential to the management of PCOS.

Management of PCOS

Given the multifaceted nature of the syndrome, it is understandable that there is no one-size-fits all solution. Generally, management approaches involve lifestyle modifications, medications, and in some cases, surgical interventions. Furthermore, treating co-morbidities related to PCOS, such as obesity, T2DM and metabolic syndrome should be managed as per recommended guidelines regardless of PCOS diagnosis⁸. Women with PCOS have a two-threefold increased risk of related co-morbidities when compared to women without PCOS, with the onset occurring years earlier than other women. Thus, when investigating for co-morbidities, it is essential to consider the increased risk associated with PCOS⁸.

The focus of management can be on alleviating symptoms such as hirsutism or addressing associated risk factors such as cardiovascular disease. Management principles may also differ based on a woman's desire to conceive, as certain hormonal options may not be an option due to their contraceptive nature. The most recent evidence based international PCOS guideline updated in 2018 sets out a range of recommendations for treating PCOS-related symptoms that are core to diagnosis, namely, irregular cycles and hirsutism⁴.

Lifestyle measures

Conservative management strategies for PCOS primarily involve lifestyle modifications such as diet, exercise and behavioural interventions, aimed at achieving and maintaining a healthy weight. This is important, given that obesity leads to a worsening of symptom profile for women with PCOS⁴. These measures can improve insulin resistance, reduce symptom burden, and improve overall quality of life, given that hyperinsulinaemia promotes hyperandrogenism⁴. Physicians should recommend healthy eating and regular exercise to all patients with PCOS. A meta-analysis carried out in 2019 showed that lifestyle interventions in women with PCOS lead to an improvement in weight, free androgen index and BMI²². However, there was no specific impact on rates of live births or menstrual regularity, both of which are key considerations when it comes to PCOS management.

Patient education and signposting are important in the management of PCOS, as it can help patients understand their condition and make informed decisions about their treatment options. Information given should be culturally appropriate, evidence-based, and tailored to individual patients. Although lifestyle interventions are important for managing PCOS, adherence to these measures can be challenging. Compliance with lifestyle modifications is crucial to achieve goals such as weight loss, and the effectiveness of these interventions may decrease over time if adherence is not maintained²³. Given the negative psychological effects associated with PCOS, physicians should consider the need for psychological support, such as support groups or talking therapies such as cognitive behavioural therapy, which may be effective in women with PCOS²⁴. A randomised trial conducted in 2015 showed that a three-pronged treatment strategy, including diet modifications, exercise and CBT improved depression and self-esteem in obese women with PCOS²⁵.

Medications

Pharmacological management is often used as a second-line treatment for PCOS, after lifestyle interventions. The medication chosen depends

on various factors, including the patient's fertility goals, primary concerns, and comorbidities such as T2DM. Medical options may include oral contraceptives, insulin sensitisers, and anti-androgen medications. Combined oral contraceptives (COCs) have proven effective in treating menstrual irregularities and are superior to progestin-only preparations in managing hirsutism and acne⁸. However, patients must be counselled on the potential side effects and risks, such as mood disturbances and increased risk of thromboembolism.

Metformin is another medical option that has shown to improve menstrual regularity, increase insulin sensitivity, and reduce hyperandrogenism, particularly when used in combination with lifestyle modifications, even in women without T2DM²⁶. However, patients should be aware of the potential gastrointestinal side effects that may impact compliance. Modified-release preparations of metformin may help alleviate these symptoms⁴.

Anti-androgen medications such as spironolactone are also an option. Spironolactone is an aldosterone antagonist that primarily acts as a diuretic, but can also lower androgen levels and improve PCOS symptom profile. The medication's anti-androgenic effects come from the blockade of androgenic receptors, which partly obstructs adrenal steroidogenesis and blocks the enzyme 5 α reductase, thereby increasing the level of sex hormone-binding globulin protein in the bloodstream, which binds to androgens²⁷. However, spironolactone is not recommended for use during pregnancy or for those trying to conceive, as it is associated with feminisation of the male fetus in animal studies^{27,28}. Hence, it is recommended to be taken in combination with an oral contraceptive.

Surgical interventions

Surgical management options for PCOS are not commonly recommended and are generally considered after conservative and medical methods have been exhausted. These options include ovarian drilling, laparoscopic ovarian surgery, and bariatric surgery for those with severe obesity⁴. Ovarian drilling is a procedure that uses a laser beam or a surgical needle,

administered laparoscopically, to destroy small areas of ovarian tissue. This can reduce androgen production and restore ovulation in some patients who have not responded to medical methods of ovulation induction, such as clomiphene citrate⁸. However, the evidence for the effectiveness of ovarian drilling is limited, as a Cochrane Review in 2020 found that it may decrease the live birth rate in women with anovulatory PCOS and clomiphene citrate resistance compared with medical ovulation induction alone²⁹. Additionally, patients undergoing ovarian drilling are exposed to the risks associated with surgery, such as infection, abdominal adhesions, and thrombosis.

In cases of severe obesity, bariatric surgery may be considered for patients with a BMI over 40 or over 35 with comorbidities. This surgery can lead to weight loss, improve insulin resistance and ovulation, and reduce symptoms of PCOS³⁰. However, bariatric surgery is not without risks, and patients should be carefully selected and assessed for the procedure. Potential risks include surgical complications, nutritional deficiencies, and the need for long-term follow-up care⁴.

Conclusion

While significant progress has been made in understanding PCOS, several research questions remain. For instance, there is a need for further investigation into the aetiology of PCOS, including the role of genetic and environmental factors, to aid in earlier diagnosis and treatment. Additionally, while some therapies have been effective in managing the symptoms of PCOS, their long-term efficacy and safety remain uncertain. There is a need to better understand the long-term health consequences of PCOS, particularly regarding cardiovascular disease and cancer risk.

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healthcare providers, and patient advocacy groups. This may involve developing new tools and technologies for diagnosis and treatment, as well as exploring novel interventions and therapies. There is a growing recognition of the importance of PCOS as a major health issue affecting millions of women worldwide, and continued research efforts will be critical for improving diagnosis, treatment, and long-term outcomes for those affected by the condition.

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