TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2024;11(1):9-12
DOI: 10.4274/tmsj.galenos.2024.2023-11-1

REVIEW

POLYCYSTIC OVARY SYNDROME (PCOS) PATHOGENESIS, DIAGNOSIS, AND COMMON TREATMENT OPTIONS: A LITERATURE REVIEW

İlayda Karakoç

Medipol University School of Medicine, İstanbul, TÜRKİYE

ABSTRACT

Polycystic ovary syndrome stands out among other syndromes in women of reproductive age in terms of prevalence. It can be identified with the presence of at least two of these three key symptoms: irregular cycles, hyperandrogenism, and polycystic ovary morphology. Even though the etiology is uncertain, the syndrome occurs due to both genetic and environmental factors. Additionally, polycystic ovary syndrome comes with other comorbidities such as infertility, thyroid diseases, abdominal obesity, insulin resistance, and diabetes. Its multifactorial nature with different clinical representations, requires various alternatives for treatment and symptom management. This review aims to understand the underlying causes of the syndrome and to correlate this understanding with symptom management approaches.

Keywords: Hyperandrogenism, ovulation, polycystic ovary syndrome

INTRODUCTION

Polycystic ovary syndrome (PCOS) stands out among other syndromes in women of reproductive age in terms of prevalence (1). There are three key symptoms to identify PCOS: irregular cycles, hyperandrogenism, and polycystic ovary morphology (PCOM) (1). In 1935 Stein and Leventhal (2) identified this condition in their paper titled "Amenorrhea Associated with Bilateral Polycystic Ovaries". They found that PCOM is correlated with several other major and minor manifestations. According to their study, these manifestations are amenorrhea, oligomenorrhea, infertility, masculinizing changes such as hirsutism, goiter, and obesity (2). Due to the history and manifestation of the syndrome, PCOS can be named "Stein-Leventhal syndrome" or "hyperandrogenic anovulation". Despite the diagnostic criteria having slight changes and additions, the same characteristics are used for both identification and diagnosis (1, 2). Even though the etiology is not certain, it is known that both environmental factors and genetics play a role in this manifestation (3, 4). Parallel to PCOS, some other conditions such as infertility, thyroid diseases, abdominal obesity, insulin resistance (IR), and diabetes may occur (4). Due to its multifactorial nature with different clinical presentations, there is a wide range of options for treatment and symptom management (5). This review aims to understand the underlying structure of the syndrome and to correlate this understanding with symptom management approaches.

Epidemiology

Polycystic ovary syndrome is considered a multifactorial and heterogenous syndrome (4, 6). It is known that the diagnosis rate of females who have this syndrome can be 6-20%, depending on the population (4). One study suggests that 35% of the mothers and 40% of the sisters of premenopausal untreated PCOS patients also have the syndrome, proving the effect of genetics (7). It is also mentioned that single nucleotide polymorphism and epigenetic modifications due to exposures are also contributing to the prevalence (8). Lifestyle, socioeconomic status, and

Address for Correspondence: İlayda Karakoç, Medipol University School of Medicine, İstanbul, TÜRKİYE
e-mail: ilaydakrkc@gmail.com
ORCID iD of the author: 0000-0002-1118-1260.
Received: 03.11.2023 Accepted: 03.02.2024

Cite this article as: Karakoç İ. Polycystic ovary syndrome (PCOS) pathogenesis, diagnosis, and common treatment options: a literature review. Turk Med Stud J 2024;11(1):9-12.

environmental factors have an impact on this situation as well (7, 9). Prevalence may vary between populations. The severity of symptoms also varies between races (9). Hirsutism can be given as an example of symptoms that differ in severity as it is found that hirsutism is more common and severe in South Asian, Indian, Mediterranean, and Middle Eastern women than in some of the Caucasian races and East Asian women (9).

Diagnosis

Core diagnostic criteria of PCOS are the presence of at least two out of the following three elements: hyperandrogenism, ovulatory dysfunction, and PCOM (1, 10). IR and obesity are common, yet they do not directly indicate the presence of the syndrome (10).

Hyperandrogenism is divided into two main categories: biochemical and clinical (10). Biochemical hyperandrogenism is identified with mild to moderately elevated serum levels of androgenic precursors such as dehydroepiandrosterone sulfate (DHEAS), androstenedione (A4), and proper forms of androgens such as testosterone (T4) (11). Major clinical manifestation of hyperandrogenism is hirsutism, whereas alopecia and acne are the minor clinical manifestations (10, 11). Hirsutism can be assessed by the Ferriman-Gallwey index by scoring the growth of hair from 0 to 4 hair in the chest, chin, upper lip, upper arm, upper and lower back, upper and lower abdomen, and thighs (10). If this index is greater than a total score of 4 to 6, it can be identified as hirsutism (10).

Ovulatory dysfunction clinically represents itself with amenorrhea, which means the absence of menstruation, or oligomenorrhea that is defined as 35 days or more between menstrual cycles or less than 8 cycles a year (1, 10). It is caused by a deficiency of follicle-stimulating hormone (FSH) and overproduction of luteinizing hormone (LH), leading follicles to mature into antral follicles, yet not causing enough stimulation for ovulation (3).

Polycystic ovary morphology context covers ultrasound images with more than 12 follicles per ovary, and/or more than 20 follicles in both ovaries with an ovarian volume greater than 10 cm^3 (1). Primordial follicles grow into preantral and antral follicles, causing PCOM (12). LH, FSH, and estradiol levels have additional significance in diagnosis (13). Increased LH to FSH ratio is especially significant due to the increased gonadotropin hormone-releasing hormone (GnRH) pulse frequency, indicating the presence of the syndrome (3, 13). This situation mainly occurs due to excess LH and ovarian androgens or excess LH stimulation (3, 12).

Studies suggest that having PCOM does not imply having PCOS directly likewise, having ovulatory dysfunction and hyperandrogenism could not be evidence alone (1, 12, 13). According to Rotterdam criteria, a patient must possess two of the three main symptoms to be diagnosed with PCOS (1). Due to the combinations of the symptoms, PCOS patients fall under 4 phenotypes (1, 10, 12):

A. Classic (Complete) PCOS: All symptoms are present,

B. Classic PCOS: Hyperandrogenism and oligo-anovulation,

C. Ovulatory PCOS: Hyperandrogenism and PCOM,

D. Non-hyperandrogenic PCOS: Oligo-anovulation and PCOM.

When these 4 phenotypes are compared, phenotypes A and B tend to show symptoms more severely (1, 10). Phenotype D is known as the mildest form and phenotype C falls between A-B and D, in terms of severity (1, 10).

Etiology and Pathogenesis

Polycystic ovary syndrome is a syndrome that is composed of multiple hereditary and environmental elements (14). Symptoms occur when inherited factors meet with environmental exposure, including heavy metals, endocrine-disrupting chemicals, and pesticides (3, 14). As an example of many endocrine-disrupting chemicals, Bisphenol A (BPA), a compound utilized in the plastic industry, is detected higher in serum concentration in PCOS patients than in healthy individuals (15). BPA disrupts the endocrine system by interacting with estrogen receptors, correlating with increased T4 and free androgen index (15). Therefore, it can be said that plastic utilization has an impact on PCOS (16). Other examples of endocrine-disrupting chemicals include perfluorooctanoate and perfluorooctane sulfonate (14).

It is also known that lifestyle greatly affects the course of PCOS (14, 16). It is found that smoking or being exposed to smoke has a relationship with oligo-anovulation (3, 16). Mitochondrial dysfunction and oxidative stress resulting from the reduction in glutathione and decreased levels of antioxidants cause the inability to reduce reactive oxygen species or toxins causing early luteinization of primordial follicles (3, 16). Snoring and obstructive sleep apnea also contribute to the condition (17). These sleep disorders are observed in PCOS patients with obesity (17). In rats, it is observed that an over-eating and high-fat diet lowers folliculogenesis and the quality of oocytes (18). It is also proven that high body mass index (BMI) is associated with PCOS, low oocyte quality, and a higher risk of miscarriage (18).

High BMI is a risk factor for both IR and central obesity (19, 20). PCOS can occur with high BMI, not correlating with sex hormone levels (19). High BMI is one of the reasons for IR (21). When IR meets with underlying genetic material for PCOS, it enhances the symptoms (21). Excessive insulin levels cause theca cells to secrete androgens which cause PCOM (3).

Genetic sisters, mothers, and fathers of PCOS patients have a higher prevalence of IR and type II diabetes (22, 23). Since insulin has an impact on the metabolic pathways of carbohydrates, proteins, and lipids, it also imitates the action of LH and causes excessive androgen output by raising GnRH pulse frequency (3, 24). Additionally, IR lowers the synthesis of sex hormone-binding globulin (SHBG) in the liver, resulting in increased free androgen levels in circulation (24).

Androgen exposure enhances the signs of PCOS. Another cause of developing PCOS more frequently is to be exposed to

high levels of prenatal androgens (24). Aromatase deficiency or abnormality is another reason for hyperandrogenism (8). Due to the lack of functioning aromatase, conversion from testosterone to estradiol drops, leading to excess androgens (8). It is important to mention that many other genes related to PCOS can be listed (8).

Anti-Müllerian hormone (AMH) is one of the indicators of PCOS. AMH is responsible for the maturation and development of follicles. Over-secretion of AMH can cause ovary malfunction (25). AMH and its receptor variants which are low functioning, cause 6.7% of PCOS cases (14).

Post-translational modifications are also contributing to the syndrome, yet these mechanisms can be used in therapeutic ways to reduce the symptoms of PCOS (26).

Fertility issues occur due to the changes in the microenvironments of the follicles, resulting in a lack of oocyte quality, and implantation issues due to the changes in the endometrium (4). As it was described, it is an endocrine disorder that can cause fertility issues, and diagnosis and symptom management are fundamental (4). Many options, such as lifestyle changes, weight loss, pharmacotherapy, and procedures such as laparoscopic ovarian surgery and assisted reproduction techniques, can help with conception (27).

Common Treatment Options

There is no cure for PCOS itself (25). Treatment options are considered for each patient individually, due to multiple mechanisms and different phenotypes (3, 25). Also, it is vital to know that lifestyle has a great impact on pathogenesis (3, 16). Modifications in daily life can be helpful for overall symptom management (3, 16). Exercising regularly and having a healthy diet help reduce BMI, which in turn helps with insulin sensitivity and increases metabolic rate, thus decreasing insulin levels (5).

Combined oral contraceptives (OCs) are the first-line drugs that are used in PCOS treatment (3, 28). They consist of estrogens and progesterone. They are primarily used to regulate menstruation and decrease the severity of hyperandrogenism symptoms (28). Another property of combined OCs is triggering the liver for the synthesis of SHBG (14). As a result of increased SHBG concentration, free T4 levels decrease. Combined OCs with progesterone are also helping with the suppression of LH secretion (28).

Antiandrogens are a group of drugs that suppress androgen effects by competitively binding to androgen receptors. Additionally, they are the first-line medication for hirsutism. Cyproterone acetate, spironolactone, and flutamide can be counted in this group (25).

Ovulation inducers are a suitable form of treatment for anovulatory sterility caused by PCOS (3, 27). Clomiphene citrate, a first-line medication for ovulatory dysfunction, competitively binds to estrogen receptors at the hypothalamus and pituitary level, turns down the negative feedback effect of estrogen, and increases FSH (25). Aromatase inhibitors are also effective for ovulatory dysfunction because they prevent the conversion of T4 to estradiol, causing positive feedback on the hypothalamic-pituitary-ovarian axis (3). This positive feedback results in GnRH secretion, followed by FSH release and follicular stimulation (3).

Insulin-sensitizing drugs are used for IR primarily (3, 5, 25). Metformin, a biguanide drug, is used as first-line and thiazolidinediones as second-line medication (25). When insulin levels normalize, the severity of the symptoms decreases, and the menstruation cycle improves (29). Insulin sensitization reduces insulin levels, reverting the negative effects of insulin on ovaries (3).

Inositol is a carbocyclic sugar that can be used as a dietary supplement with a low risk of adverse effects (5). It works as a secondary messenger in important mechanisms such as thyroid-stimulating hormone or glycogen synthesis (3). Two of many types of inositol are discussed for PCOS. One is myo-inositol, which acts on glucose intake and metabolism while taking part in FSH signaling. The other is D-chiro-inositol, which controls glycogen synthesis and is effective in androgen production caused by hyperinsulinemia (30).

CONCLUSION

Polycystic ovary syndrome is a multifactorial and heterogeneous syndrome affecting women of all age groups (4, 6). It has three main criteria: irregular cycles, hyperandrogenism, and PCOM (1). PCOS is composed of multiple hereditary and environmental elements (14). Due to its multifactorial nature patients come with different phenotypes (1, 3). In addition to infertility, thyroid diseases, abdominal obesity, IR, and diabetes may occur, depending on the patient (4). There is no cure for the syndrome itself and treatment options should be evaluated for each patient individually (3, 25). Lifestyle and habits take a great place in pathogenesis, positive changes in daily life can be beneficial for the individual (3, 16).

Ethics Committee Approval: *N/A*

Informed Consent: *N/A*

Financial Disclosure: *The author declared that this study received no financial support.*

REFERENCES

1. Christ JP, Cedars MI. Current guidelines for diagnosing PCOS. Diagnostics (Basel) 2023;13(6):1113. [Crossref]
2. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 1935;29(2):181-91. [Crossref]
3. Singh S, Pal N, Shubham S et al. Polycystic ovary syndrome: etiology, current management, and future therapeutics. J Clin Med 2023;12(4):1454. [Crossref]
4. Siddiqui S, Mateen S, Ahmad R et al. A brief insight into the etiology, genetics, and immunology of polycystic ovarian syndrome (PCOS). J Assist Reprod Genet 2022;39(11):2439-73. [Crossref]
5. Akre S, Sharma K, Chakole S et al. Recent advances in the management of polycystic ovary syndrome: a review article. Cureus 2022;14(8):e27689. [Crossref]

6. Mirza FG, Tahlak MA, Rjeili RB et al. Polycystic ovarian syndrome (PCOS): does the challenge end at conception? Int J Environ Res Public Health 2022;19(22):14914. [Crossref]
7. Kahsar-Miller MD, Nixon C, Boots LR et al. Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS. Fertil Steril 2001;75(1):53-8. [Crossref]
8. Ajmal N, Khan SZ, Shaikh R. Polycystic ovary syndrome (PCOS) and genetic predisposition: a review article. Eur J Obstet Gynecol Reprod Biol X 2019;3:100060. [Crossref]
9. VanHise K, Wang ET, Norris K et al. Racial and ethnic disparities in polycystic ovary syndrome. Fertil Steril 2023;119(3):348-54. [Crossref]
10. Mumusoglu S, Yildiz BO. Polycystic ovary syndrome phenotypes and prevalence: differential impact of diagnostic criteria and clinical versus unselected population. Curr Opin Endocr Metab Res 2020;12:66-71. [Crossref]
11. Cussen L, McDonnell T, Bennett G et al. Approach to androgen excess in women: clinical and biochemical insights. Clin Endocrinol (Oxf) 2022;97(2):174-86. [Crossref]
12. Rosenfield RL. The polycystic ovary morphology-polycystic ovary syndrome spectrum. J Pediatr Adolesc Gynecol 2015;28(6):412-9. [Crossref]
13. Mortensen M, Ehrmann DA, Littlejohn E et al. Asymptomatic volunteers with a polycystic ovary are a functionally distinct but heterogeneous population. J Clin Endocrinol Metab 2009;94(5):1579-86. [Crossref]
14. Rosenfield RL. Current concepts of polycystic ovary syndrome pathogenesis. Curr Opin Pediatr 2020;32(5):698-706. [Crossref]
15. Konieczna A, Rachoń D, Owczarek K et al. Serum bisphenol A concentrations correlate with serum testosterone levels in women with polycystic ovary syndrome. Reprod Toxicol 2018;82:32-7. [Crossref]
16. Zhang B, Zhou W, Shi Y et al. Lifestyle and environmental contributions to ovulatory dysfunction in women of polycystic ovary syndrome. BMC Endocr Disord 2020;20(1):19. [Crossref]
17. Kahal H, Kyrou I, Uthman OA et al. The prevalence of obstructive sleep apnoea in women with polycystic ovary syndrome: a systematic review and meta-analysis. Sleep Breath 2020;24(1):339-50. [Crossref]
18. Sohrabi M, Roushandeh AM, Alizadeh Z et al. Effect of a high fat diet on ovary morphology, in vitro development, in vitro fertilisation rate and oocyte quality in mice. Singapore Med J 2015;56(10):573-9. [Crossref]
19. Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012;33(6):981-1030. [Crossref]
20. Ibáñez L, de Zegher F. Adolescent PCOS: a postpubertal central obesity syndrome. Trends Mol Med 2023;29(5):354-63. [Crossref]
21. Barber TM. Why are women with polycystic ovary syndrome obese? Br Med Bull 2022;143(1):4-15. [Crossref]
22. Guarnotta V, Lucchese S, Mineo MI et al. Predictive factors of polycystic ovary syndrome in girls with precocious pubarche. Endocr Connect 2021;10(7):796-804. [Crossref]
23. Yilmaz B, Vellanki P, Ata B et al. Diabetes mellitus and insulin resistance in mothers, fathers, sisters, and brothers of women with polycystic ovary syndrome: a systematic review and meta-analysis. Fertil Steril 2018;110(3):523-33. [Crossref]
24. Witchel SF, Oberfield SE, Peña AS. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. J Endocr Soc 2019;3(8):1545-73. [Crossref]
25. Bulsara J, Patel P, Soni A et al. A review: brief insight into polycystic ovarian syndrome. Endocr Metab Sci 2021;3:100085. [Crossref]
26. Wei H, Huo P, Liu S et al. Posttranslational modifications in pathogenesis of PCOS. Front Endocrinol (Lausanne) 2022;13:1024320. [Crossref]
27. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. Hum Reprod 2008;23(3):462-77. Erratum in: Hum Reprod 2008;23(6):1474. [Crossref]
28. de Melo AS, Dos Reis RM, Ferriani RA et al. Hormonal contraception in women with polycystic ovary syndrome: choices, challenges, and noncontraceptive benefits. Open Access J Contracept 2017;8:13-23. [Crossref]
29. Geller DH, Pacaud D, Gordon CM et al. State of the art review: emerging therapies: the use of insulin sensitizers in the treatment of adolescents with polycystic ovary syndrome (PCOS). Int J Pediatr Endocrinol 2011;2011(1):9. [Crossref]
30. Gateva A, Unfer V, Kamenov Z. The use of inositol(s) isomers in the management of polycystic ovary syndrome: a comprehensive review. Gynecol Endocrinol 2018;34(7):545-50. [Crossref]