The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 4979- 4983

Epidemiology, Risk Factors, Pathogenesis and Etiology of Polycystic Ovarian Syndrome: Review Article

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ABSTRACT
A prevalent endocrine illness that primarily affects women of reproductive age are affected by the disorder known as polycystic ovarian syndrome (PCOS). In addition to psychological dysfunction, clinical signs include hyperandrogenism, anovulation, infertility, and a higher risk of metabolic disorders. The epidemiology, risk factors, pathophysiology, and etiology of PCOS are all covered in this review.

INTRODUCTION
Between 6% and 10% of women in developed nations are believed to have PCOS, according to a number of attempts to estimate the frequency of polycystic ovaries in research done in the neighborhood. In Britain, up to 52% of South Asian immigrant women come from underdeveloped countries. According to ultrasound findings, 20% of reproductive-age women have polycystic ovaries, and 50% of them exhibit biochemical or clinical indicators of anovulation or excess androgen **(1).**

According to the Rotterdam criteria, Egypt had a PCOS prevalence of between 14.5% and 37.5%. This incidence is more prevalent in populations that are at higher risk for the metabolic syndrome and insulin resistance. Strong data suggest that women with PCOS may benefit from early diagnosis and treatment for a variety of conditions also develop type II diabetes and cardiovascular disease **(2).**

Risk factors:
1- One risk factor for PCOS is a family history of the condition. The idea that PCOS is a heritable condition is based on the tendency for instances to cluster in families. It may be genetically influenced if PCOS or its symptoms are more common in first-degree relatives. Additionally, monozygotic twins have been shown to have higher concordance than dizygotic twins. Obstacles to progress in this area include prepubescent girls, postmenopausal women, and the challenge of getting large enough sample sizes to allow for adequate statistical power. Several diseases are linked to PCOS prevalence increase **(3)**.

2- It is commonly acknowledged that obesity is a serious global pandemic with far-reaching health consequences. Obesity prevalence has dramatically increased in wealthy countries, and this trend is now becoming seen in underdeveloped countries. Body mass index (BMI) is used by the World Health Organization (WHO) to determine an individual's normal weight of 18.5–24.99 kg/m^2, overweight with a BMI of 25-29.99 kg/m^2, and obese with a BMI of 30 kg/m^2 or more **(4).**

3- The development of PCOS clinical symptoms typically occurs before a history of weight gain symptoms, and adopting a healthy lifestyle has been found to help women with PCOS lose body weight, abdomen fat, testosterone, increase insulin sensitivity, and reduce hirsutism **(5).**

4- It has been demonstrated that environmental variables contribute to the pathophysiology of PCOS. Numerous researches have looked at the relationship between socioeconomic status (SES) and unhealthy habits like smoking, eating poorly, and not exercising. Obesity, which has a high rate of co-morbidity with PCOS, is one of the most frequently seen relationships with low SES **(6).**

Pathogenesis and Etiology of PCOS:
PCOS manifests as a phenotype at the time of diagnosis, reflecting a vicious cycle combining ovarian, neuroendocrine, and metabolic abnormalities. Numerous theories explaining the proximal physiological causes of PCOS have been put out through time **(8).**

The phenotypic approach to classifying PCOS was proposed by the National Institutes of Health (NIH) consensus group **(9)** as follows:

1. Phenotype A (full-blown syndrome PCOS: HA+OD+PCO) consists of ovulatory dysfunction (OD), polycystic ovaries (PCO), and HA (clinical or biochemical).
2. Phenotype B (non-PCO PCOS: HA+OD) is composed of hyperandrogenism (HA) and ovulatory dysfunction (OD).
3. The components of PCO and HA make up phenotype C (ovulatory PCOS: HA+PCO).
4. PCO and OD make up phenotype D (non-hyperandrogenic PCOS: OD+PCO).

Received: 06/06/2022
Accepted: 11/08/2022

The four phenotypes presented here may or may not represent the complete range of PCOS they are associated with. There hasn't been enough research done to examine the various PCOS phenotypes [10].

Pathophysiology:

PCOS has a complicated underlying pathophysiology that is probably varied among those who are affected. The ovarian-pituitary-ovarian axis has several dysfunctions [11].

1. PCOS's pathophysiology is associated with psychological diseases like anxiety and depression as well as reproductive and metabolic disorders.
2. Gonadotropin stimulation is necessary for ovarian steroid generation. The adverse consequences of ovarian steroids, which are most likely brought on by an overdose of testosterone (given that the androgen receptor blocker flutamide may be able to reverse them), do not affect the PCOS women's gonadotropin-releasing hormone (GnRH) pulse generator. A major contributing element to the hyperandrogenaemia experienced by women with PCOS is the hypersecretion of luteinizing hormone (LH) as a result of the increased GnRH pulse frequency. LH drives theca cell hyperandrogenism.
3. Hyperinsulinemia, which worsens LH overexpression, lowers SHBG production in the liver, and stimulates the release of testosterone from theca cells, causes blood hyperandrogenism to rise. Follicle-stimulating hormone (FSH) levels decreased release prevents follicles from growing larger and maturing.
4. An excessive amount of preantral and tiny antral follicles results in the generation of anti-Müllerian hormone (AMH). AMH prevents the aromatase gene, CYP19A1, from being expressed, which prevents androgens from being converted to estrogens and contributes to higher androgen levels. Increased GnRH neuron activity and LH production, which is regulated by GnRH, are both directly stimulated by elevated AMH levels, which may further promote ovarian hyperandrogenism.
5. By promoting androgen production in theca cells, ovarian hyperandrogenism is made worse by high levels of luteinizing hormone (LH), which are brought on by increased gonadotropin-releasing hormone (GnRH) secretion and possibly also by the absence of progesterone's antagonistic effects. Further mechanistic researches are needed because it is still unclear whether hyperandrogenism or hyperinsulinemia is the main contributor of PCOS [9].

Clinical Picture of PCOS:

a) Irregular cycles and abnormal ovulation:

Common monthly irregularities, linked oligomenorrhea, amenorrhea, and prolonged irregular bleeding are all related to PCOS. On the other hand, 30% of women with PCOS will have regular menstruation. PCOS affects 30%–40% of 85%–90% of women with oligomenorrhea and those with amenorrhea [12].

Irregular menstrual cycles are defined as [13]:

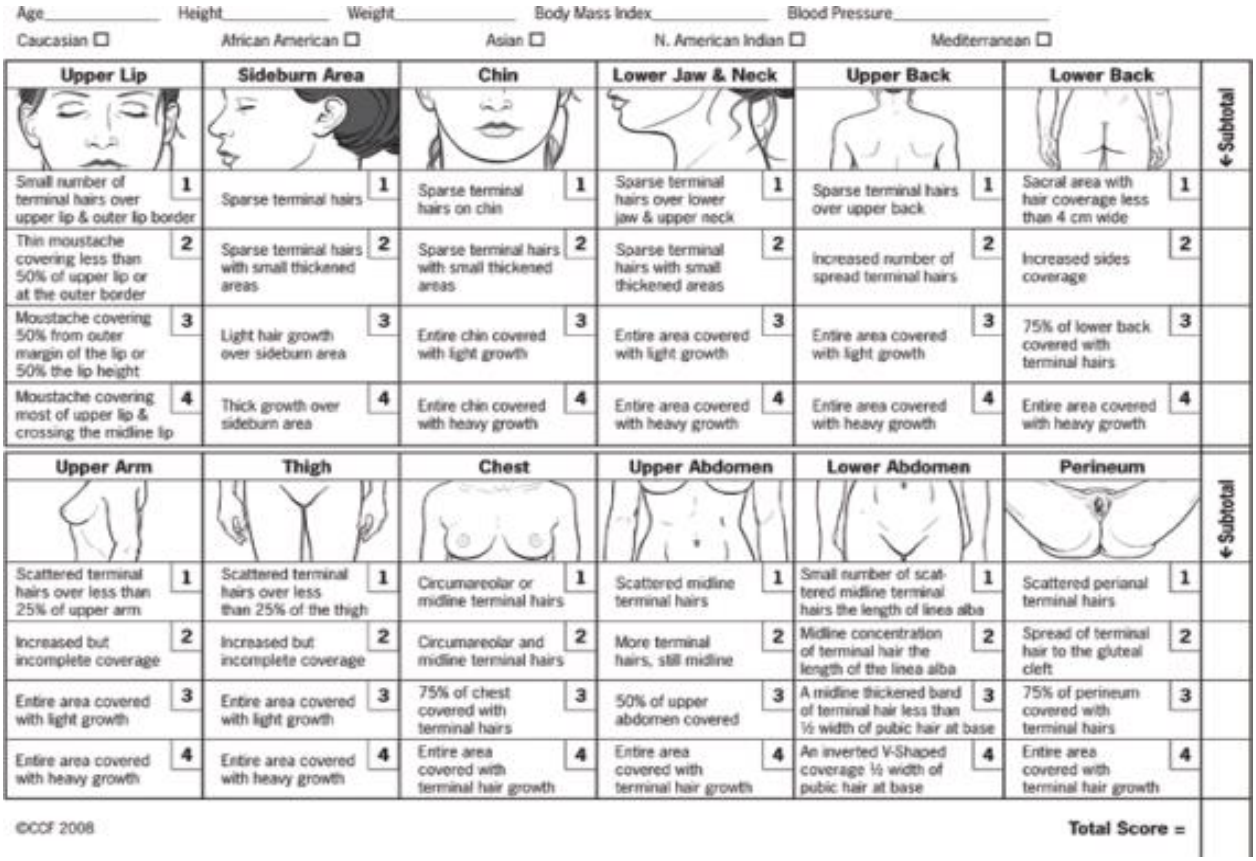
- Typical in the first year after menarche
- 1-3 years following menarche: <21 or >45 days
- From perimenopause to three years after menarche: <21 days or >35 days or <8 cycles per year
- Any menstrual cycle lasting longer than 90 days in a row >1 year post menarche.

• Even with regular cycles, ovulatory dysfunction can still happen. By taking timely measurements of progesterone concentrations, anovulation can be verified.

The diagnosis of PCOS should be taken into consideration and evaluated in accordance with the recommendations when irregular periods are observed [14].

Clinical hyperandrogenism:

To look through for clinical hyperandrogenism symptoms and signs, such as acne, alopecia, and hirsutism, as well as for severe acne and hirsutism in teenagers, a history and physical examination should be conducted. Utilizing the Ferriman-Gallwey score, hirsutism is assessed. According to the Ferriman-Gallwey scoring system, the examiner grades the subjects on a scale of 0–4 for terminal hair growth on eleven different body areas. An 8 or above on the Ferriman-Gallwey test was regarded as indicative of hirsutism. The primary tool for the clinical assessment of the modified Ferriman-Gallwey (MFG) score for facial and terminal hair development is hirsutism, and it is determined by a complete physical examination that focuses on virilization symptoms (such as acne, clitoromegaly, breast shrinkage, frontal baldness, loss of feminine physical traits, increased muscularity) [14].



Age_____ Height_____ Weight_____ Body Mass Index_____ Blood Pressure_____

Caucasian ☐ African American ☐ Asian ☐ N. American Indian ☐ Mediterranean ☐

Upper Lip	Sideburn Area	Chin	Lower Jaw & Neck	Upper Back	Lower Back	← Subtotal
Small number of terminal hairs over upper lip & outer lip border 1	Sparse terminal hairs 1	Sparse terminal hairs on chin 1	Sparse terminal hairs over lower jaw & upper neck 1	Sparse terminal hairs over upper back 1	Sacral area with hair coverage less than 4 cm wide 1	
Thin moustache covering less than 50% of upper lip or at the outer border 2	Sparse terminal hairs with small thickened areas 2	Sparse terminal hairs with small thickened areas 2	Sparse terminal hairs with small thickened areas 2	Increased number of spread terminal hairs 2	Increased sides coverage 2	
Moustache covering 50% from outer margin of the lip or 50% the lip height 3	Light hair growth over sideburn area 3	Entire chin covered with light growth 3	Entire area covered with light growth 3	Entire area covered with light growth 3	75% of lower back covered with terminal hairs 3	
Moustache covering most of upper lip & crossing the midline lip 4	Thick growth over sideburn area 4	Entire chin covered with heavy growth 4	Entire area covered with heavy growth 4	Entire area covered with heavy growth 4	Entire area covered with heavy growth 4	

Upper Arm	Thigh	Chest	Upper Abdomen	Lower Abdomen	Perineum	← Subtotal
Scattered terminal hairs over less than 25% of upper arm 1	Scattered terminal hairs over less than 25% of the thigh 1	Circumareolar or midline terminal hairs 1	Scattered midline terminal hairs 1	Small number of scattered midline terminal hairs the length of linea alba 1	Scattered perianal terminal hairs 1	
Increased but incomplete coverage 2	Increased but incomplete coverage 2	Circumareolar and midline terminal hairs 2	More terminal hairs, still midline 2	Midline concentration of terminal hair the length of the linea alba 2	Spread of terminal hair to the gluteal cleft 2	
Entire area covered with light growth 3	Entire area covered with light growth 3	75% of chest covered with terminal hairs 3	50% of upper abdomen covered 3	A midline thickened band of terminal hair less than ½ width of pubic hair at base 3	75% of perineum covered with terminal hairs 3	
Entire area covered with heavy growth 4	Entire area covered with heavy growth 4	Entire area covered with terminal hair growth 4	Entire area covered with terminal hair growth 4	An inverted V-Shaped coverage ½ width of pubic hair at base 4	Entire area covered with terminal hair growth 4	

©CCF 2008 **Total Score =**

Figure (1): Hirsutism scoring system [15]

b) Biochemical hyperandrogenism:

1- If total or free testosterone levels are not increased, androstenedione and dehydroepiandrosterone sulfate (DHEAS) may be considered but they don't add much to the diagnosis of PCOS.

2- It is impossible to adequately identify biochemical hyperandrogenism due to effects on sex hormone-binding globulin and altered gonadotropin-dependent androgen synthesis in women using hormonal contraception.

3- Calculated free testosterone, calculated bioavailable testosterone, or calculated free androgen index should be used to evaluate biochemical hyperandrogenism in the diagnosis of PCOS.

4- Evaluation of biochemical hyperandrogenism is most helpful in making a diagnosis of PCOS and/or a phenotype when the presence of clinical indications of hyperandrogenism, such as hirsutism, is ambiguous or nonexistent [16].

c) Clinical hyperandrogenism:

In order to look for symptoms and indicators of clinical hyperandrogenism, such as severe acne and hirsutism, a complete history and physical examination should be conducted in adolescents. The main tool for diagnosing hirsutism clinically is the MFG score for face and terminal hair development [17].

Ultrasound and ovarian morphology in polycystic ovarian disease (PCOM): [18].

When diagnosing PCOS in people with gynecological ages, use of ultrasonography should not < 8 years (< 8 years after menarche), because multi-follicular ovaries are very common at this period of life.

If the patient engages in sexual behavior and the procedure is suitable to the patient: -

- For PCOS diagnosis, transvaginal ultrasound is preferable.
- Using frequency-broadened endovaginal ultrasound transducers of at least 8 MHz and a follicle count per ovary, the PCOM threshold should be on either ovary. > 20 and/or a volume of the ovary less than 10 ml, indicating the absence of cysts, corpora lutea, or dominant follicles. When using outdated equipment, the PCOM threshold can be an ovarian volume ≥ 10 ml on either ovary.
- Individuals with hyperandrogenism and irregular menstrual cycles do not always need an ovarian ultrasound to be diagnosed with PCOS, but the test will still show the full spectrum of the condition.

• Transabdominal ultrasound reporting should concentrate due to the method's inconsistent follicle number determination on ovarian volume with a 10 ml criterion.

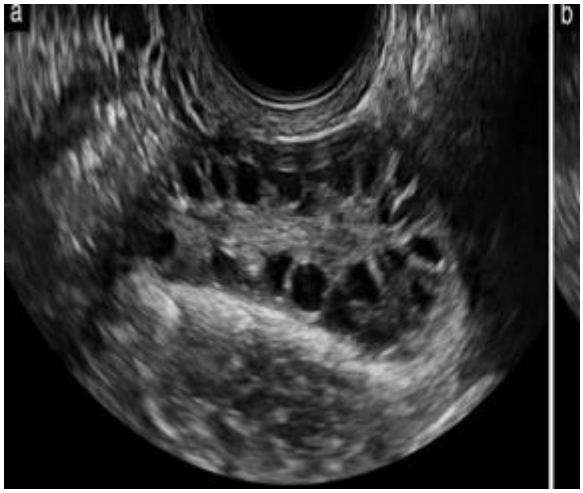


Figure (2): Two-dimensional grayscale ultrasound scans of the right and left ovaries of a 24-year-old nulligravida show a large number of antral follicles on the periphery and a relatively hyperechoic ovarian stroma in the middle [(19)]

Clinical picture and diagnostic work up of PCOS:

Table (1): Diagnostic criteria for PCOS according to the NIH conference, the revised criteria from the ESHRE/ASRM sponsored consensus meeting and the criteria of the Androgen Excess Society [(20)]

NIH criteria	Rotterdam criteria	Androgen Excess and PCOS Society
Must include all the following: – Hyperandrogenism and/or hyperandrogenemia – Anovulation or oligo-ovulation	Must include two of the following: – Anovulation or oligo-ovulation – Clinical and/or biochemical signs of hyperandrogenism – PCOM	Requires all the following: – Hirsutism and/or hyperandrogenemia – Oligo-ovulation and/or PCOM

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest: There are no conflicts of interest, according to the authors.

REFERENCES

1. **Skiba A, Bell J, Herbert D *et al.* (2021):** Use of community-based reference ranges to estimate the prevalence of polycystic ovary syndrome by the recognised diagnostic criteria, a cross-sectional study. *Human Reproduction*, *36*(6): 1611-1620.
2. **Abd Elmonem H, Hammad K, Ghanem I *et al.* (2022):** Prevalence, phenotypic distribution, and clinical characteristics of polycystic ovary syndrome in Egyptian women with type 1 diabetes mellitus. *Journal of Medicine in Scientific Research*, *5*(1): 51-55.
3. **Carson A, Kallen N (2021):** Diagnosis and management of infertility: a review. *Jama*, *326*(1): 65-76.
4. **Zundel N, Hernandez D, Gagner M (2020):** Laparoscopic sleeve gastrectomy: technique and outcomes. *The ASMBS Textbook of Bariatric Surgery*, 149-159.
5. **Witchel F, Oberfield E, Peña S (2019):** Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. *Journal of the Endocrine Society*, *3*(8): 1545-1573.
6. **Suresh D, Jayaseelan V, Sulgante S *et al.* (2020):** The burden of the probable polycystic ovarian syndrome and its associated factor among college going late adolescents and young adults: a cross sectional analytical study in urban Puducherry, South India. *International Journal of Adolescent Medicine and Health*, *34*(5): 337-342.
7. **Stener-Victorin E, Deng Q (2021):** Epigenetic inheritance of polycystic ovary syndrome—challenges and opportunities for treatment. *Nature Reviews Endocrinology*, *17*(9): 521-533.
8. **Rosenfield L (2020):** Current concepts of polycystic ovary syndrome pathogenesis. *Current opinion in pediatrics*, *32*(5): 698-710.
9. **Lizneva D, Suturina L, Walker W *et al.* (2016):** Criteria, prevalence, and phenotypes of polycystic ovary syndrome. *Fertility and sterility*, *106*(1): 6-15.
10. **Sachdeva G, Gainder S, Suri V *et al.* (2019):** Comparison of the different PCOS phenotypes based on clinical metabolic, and hormonal profile, and their response to clomiphene. *Indian journal of endocrinology and metabolism*, *23*(3): 326-330.
11. **Khan J, Ullah A, Basit S (2019):** Genetic basis of polycystic ovary syndrome (PCOS): current

perspectives. *The application of clinical genetics*, 12.249-260.

12. **Zehravi M, Maqbool M, Ara I (2021):** Polycystic ovary syndrome and reproductive health of women: a curious association. *International journal of adolescent medicine and health*, *33*(6): 333-337.
13. **Munro G, Critchley O, Fraser I *et al.* (2018):** The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. International Journal of Gynecology and Obstetrics, 143(3): 393-408.
14. **Teede J, Misso L, Costello F *et al.* (2018):** Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human reproduction*, *33*(9): 1602-1618.
15. **Spritzer M, Marchesan B, Santos R *et al.* (2022).** Hirsutism, normal androgens and diagnosis of PCOS. *Diagnostics*, *12*(8): 1922-1931.
16. **Amiri M, Ramezani F, Nahidi F *et al.* (2017):** Association between biochemical hyperandrogenism parameters and Ferriman-Gallwey score in patients with polycystic ovary syndrome: a systematic review and meta-regression analysis. *Clinical endocrinology*, *87*(3): 217-230.
17. **Zhang J, Bao Y, Zhou X *et al.* (2019):** Polycystic ovary syndrome and mitochondrial dysfunction. *Reproductive Biology and Endocrinology*, *17*(1): 1-15.
18. **Azziz R (2018):** Polycystic ovary syndrome. *Obstetrics and Gynecology*, *132*(2): 321-336.
19. **Nylander M, Frøssing S, Bjerre H *et al.* (2017):** Ovarian morphology in polycystic ovary syndrome: estimates from 2D and 3D ultrasound and magnetic resonance imaging and their correlation to anti-Müllerian hormone. *Acta Radiologica* , *58*(8): 997-1004.
20. **Williams T, Mortada R, Porter S (2016):** Diagnosis and treatment of polycystic ovary syndrome. *American family physician*, *94*(2): 106-113.