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Overview Of Polycystic Ovary Syndrome (PCOS)

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Abstract

PCOS, commonly known as hyperandrogenic anovulation, is a condition that affects women's ovaries. A frequent endocrine system illness that affects women of reproductive age is polycystic ovarian syndrome (PCOS), also known as hyperandrogenic anovulation (HA), or Stein-Leventhal syndrome (Evans and Riley, 1958). According to Stein and Leventhal (1935), it is a condition that develops on one or both ovaries when an estimated 10 tiny cysts with a diameter ranging from 2 to 9 mm and/or an ovarian volume greater than 10 ml are present. According to a systematic examination of women using National Institutes of Health (NIH) diagnostic criteria, 4–10% of women of reproductive age have PCOS. Recent research reveals that PCOS is a lifelong syndrome that first manifests during pregnancy, despite the fact that it was traditionally thought to be a disorder that only affected adult women. It is a syndrome that can be avoided by raising awareness among patients and healthcare professionals. Starting with its diagnosis, pathophysiology, repercussions, and treatment options, there are numerous areas of disagreement(1).

Keywords: Cyst; Pregnancy; Oestrogen; Hypothalamus; Insulin; Puberty

1. Introduction

The disease's incidence among youngsters is yet unknown, though. The financial toll of PCOS is extremely heavy. In order to test for the illness and treat its many morbidities, such as hirsutism, infertility, and diabetes mellitus, approximately 4 billion dollars are spent annually in the United States. Patients with PCOS are twice as likely to be hospitalised to the hospital as patients without it, and the Australian Health System spends more than \$800 million annually to address the disorder. PCOS, also known as Stein-Leventhal syndrome, is one of the most prevalent endocrine system disorders that afflict women of reproductive age. As a result, an accurate and early diagnosis of PCOS is essential not only to prevent future health comorbidities but also to reduce financial cost and burden. It is a condition that has been known to exist since 1935, when Stein and Leventhal (1935) first described it. It is characterised by the development of at least 10 small cysts, with a diameter ranging from 2 to 9 mm, on one or both ovaries, as well as an ovarian volume greater than 10 ml in at least one ovary. According to a systematic examination of women using National Institutes of Health (NIH) diagnostic criteria, 4–10% of women of reproductive age have PCOS. Recent data reveals that PCOS is a lifelong syndrome that first manifests during pregnancy, despite the fact that it was formerly thought to be a disorder of adult women[1].

As an oligogenic condition, PCOS is characterised by a diverse, clinical, and biochemical phenotype that is determined by the interaction of numerous genetic and environmental variables. A family history of PCOS is rather frequent, but it is unclear if this is related to the condition's genetic origin. A formal segregation study can't be done because there isn't enough phenotypic data. But according to the most recent research, PCOS tends to cluster in families in a manner similar to an autosomal dominant pattern. 8 Poor food habits and inactivity can increase environmental factors linked to PCOS (such as obesity), and pollutants and infectious diseases may also have an impact. 8 With lifestyle changes, the reproductive and metabolic symptoms of PCOS can occasionally be reversed. Management should involve regular

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follow-up visits and a planned transfer to adult care providers in addition to checking for associated comorbidities. Early detection of girls with a high propensity to develop PCOS will be made possible by comprehensive knowledge of the etiology of the condition. Adolescent PCOS will be better managed overall if tailored therapy measures are implemented on time. [2] In spite of its high occurrence, the cause of PCOS is still unknown. It has been disputed whether PCOS genuinely reflects one single condition or a number of disorders because of the variety in the representation of clinical and biochemical markers. PCOS symptoms frequently appear around puberty, however the condition's beginnings may have been pre programmed as early as during foetal development. Around 60–80% of PCOS women also experience high androgen levels, which can cause hirsutism, acne, and alopecia as clinical symptoms. By using gas chromatography tandem mass spectrometry (GC-MS/MS) and liquid chromatography tandem mass spectrometry (LC-MS/MS), it has been shown that PCOS patients have high amounts of androgens, oestrogens, sex steroid precursors, and glucuronidated androgens metabolites in their blood. PCOS is primarily caused by an overabundance of androgens in the ovaries, but the adrenals also play a role to some extent. Most anovulatory symptoms and hyperandrogenism in women are caused by polycystic ovarian syndrome (PCOS). The life-long effects of PCOS diagnosis include higher risk for endometrial cancer, metabolic syndrome, type 2 diabetes, cardiovascular disease, and infertility. Mendelian randomization studies have suggested that some occurrences, such as oestrogen receptor-positive breast cancer, are caused more directly by PCOS than others, such as type 2 diabetes and cardiovascular problems(3).

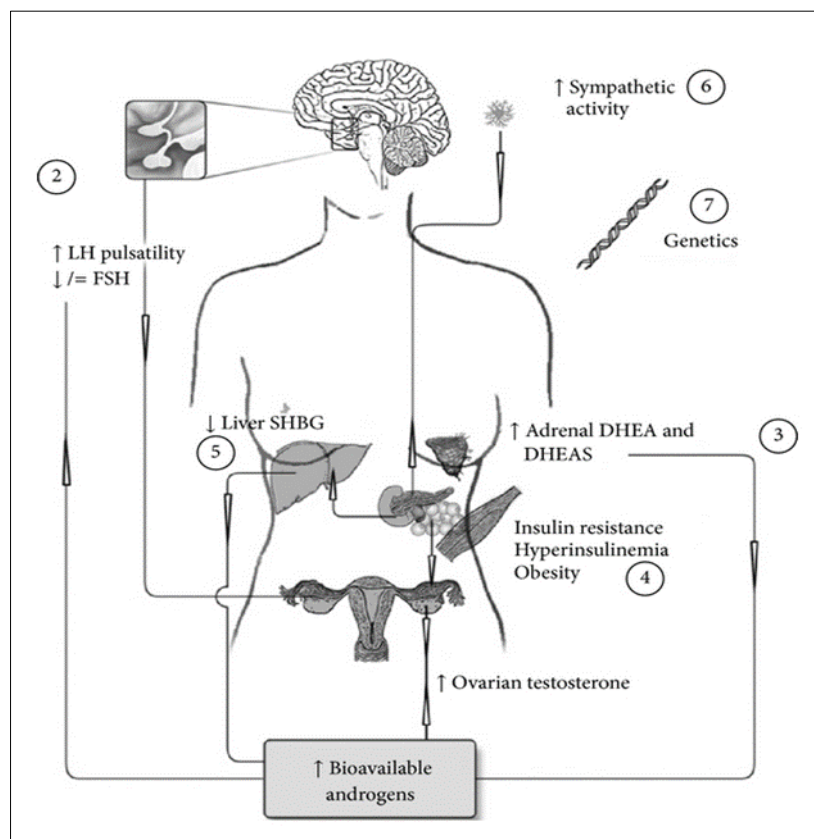


Figure 1 Complications of PCOS

2. Ovarian dysfunction in PCOS

The anomalous late phases of halted follicle growth long before predicted maturation and excessive early follicular growth in PCOS can be attributed to disrupted follicular development. One of the characteristics of PCOS, PCO morphology, is caused by this pattern of follicular development with failure in the selection of a dominant follicle for ovulation. Ovarian dysfunction in PCOS includes both the clinical repercussion of oligo-/anovulation and the morphological characteristics of polycystic ovaries, which are described as an aggregation of tiny antral follicles of size 2–9 mm. Depending on the diagnostic criteria employed, the prevalence of menstrual abnormalities, oligo-/amenorrhea in PCOS ranges from 75% to 80%. All patients will, of course, have irregular menstrual cycles if we adopt the NIH standards. In the end, it is important to recognise that irregular ovulation can lead to infertility because it makes it difficult to conceive. The most frequent reason for anovulatory infertility is PCOS. Between 90% and 95% of women who visit infertility clinics have anovulation. Nevertheless, 60% of PCOS sufferers are fertile (defined as the ability to

conceive within 12 months). [4] There are also other follicular anomalies, but androgen hypersecretion is by far the most common one. Theca and granulosa cells in the developing follicles work closely together to produce ovarian steroids, which requires gonadotropin input (Figure 2). Theca cells manufacture androstenedione from cholesterol via the CYP4 or CYP5 pathways, and it is exclusively known that granulosa cells, which contain the aromatase cytochrome P450 hydroxylase (CYP19), are responsible for the subsequent conversion to estrone and estradiol.

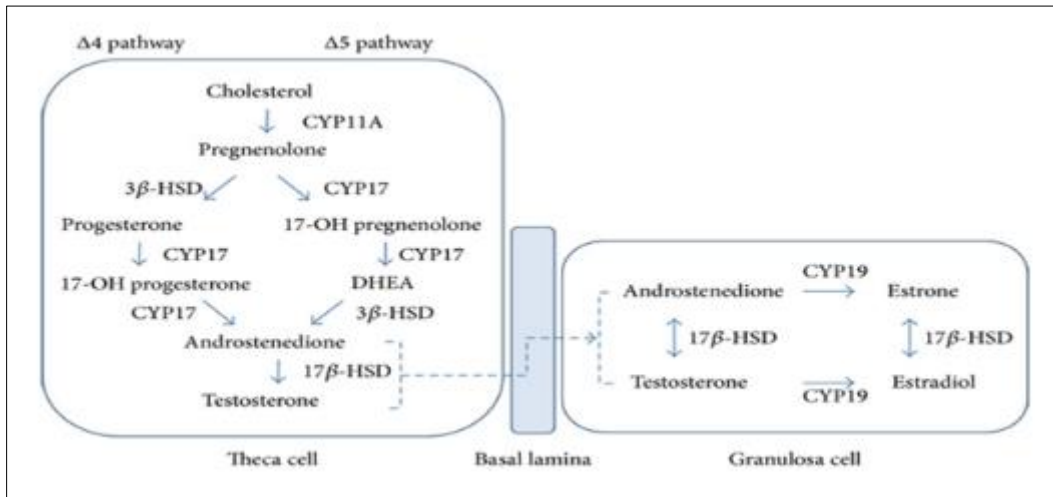


Figure 2 Diagrammatic representation of Cholesterol to Estrone

The increased androgen steroidogenesis in PCOS appears to be caused by theca interna hyperplasia, a thicker layer of theca cells. Additionally, each theca cell has a higher level of LH receptor expression and is more sensitive to LH activation. [5]

3. Insulin resistance and hypergonadism

PCOS has a complicated etiology that is still mostly unknown. The underlying hormonal imbalance caused by an excess of androgens and/or insulin, which is beyond the scope of this article, is what causes PCOS. Obesity, ovarian dysfunction, abnormalities of the hypothalamus and pituitary, as well as genetic and environmental causes of hormonal imbalances, all have a role in the development of PCOS. However, more knowledge of the pathophysiological causes of PCOS is needed.

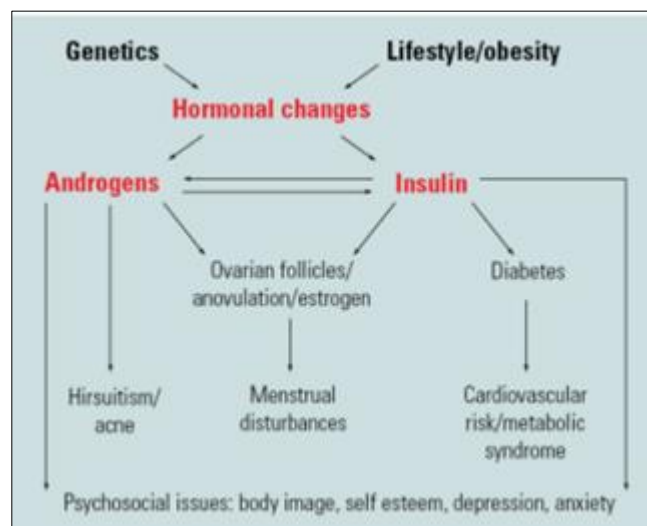


Figure 3 Insulin resistance and hyperandrogenism

The severity of hyperinsulinemia and insulin resistance in PCOS appears to be less severe when diagnosed using more recent European Society for Human Reproduction (ESHRE)/American Society of Reproductive Medicine (ASRM) standards. Insulin resistance increases androgen synthesis and increases free androgens through decreasing sex hormone binding globulin, which affects both metabolic and reproductive characteristics [15]. (SHBG). Further study is undoubtedly required in light of the murky aetiology and processes underlying insulin resistance [4].

3.1. Pathophysiology

By the time the diagnosis is made, PCOS has developed into a phenotype that reflects a vicious cycle that involves ovarian, neuroendocrine, and metabolic abnormalities. Numerous theories have been put up over the years on the proximate physiologic causes of PCOS. PCOS is a result of interactions between numerous proteins and genes that are altered by environmental and epigenetic factors. The causes of PCOS in humans and preclinical models are broken down in specific sections of this article. Major characteristics of PCOS include clinical and biochemical hyperandrogenism. Early pubertal years are when PCOS first appears. The majority of pertinent data, however, has come from clinical trials involving adult women, with a referral bias favouring the study of the more severe phenotypes. To further understand this complicated condition, preclinical models using animal and in vitro research are used in conjunction with clinical research. Recent genetic, clinical, and experimental findings underline the role of neuroendocrine systems in the pathogenesis of PCOS. factors influencing the phenotype of PCOS. PCOS affects every stage of a woman's life. Circular symbols represent factors that could have an impact on the pathophysiology of PCOS. Not every aspect has an impact on every person. PCOS is the biological embodiment of a complex network of interconnected neuroendocrine, hormonal, metabolic, genetic, and environmental factors[1,10].

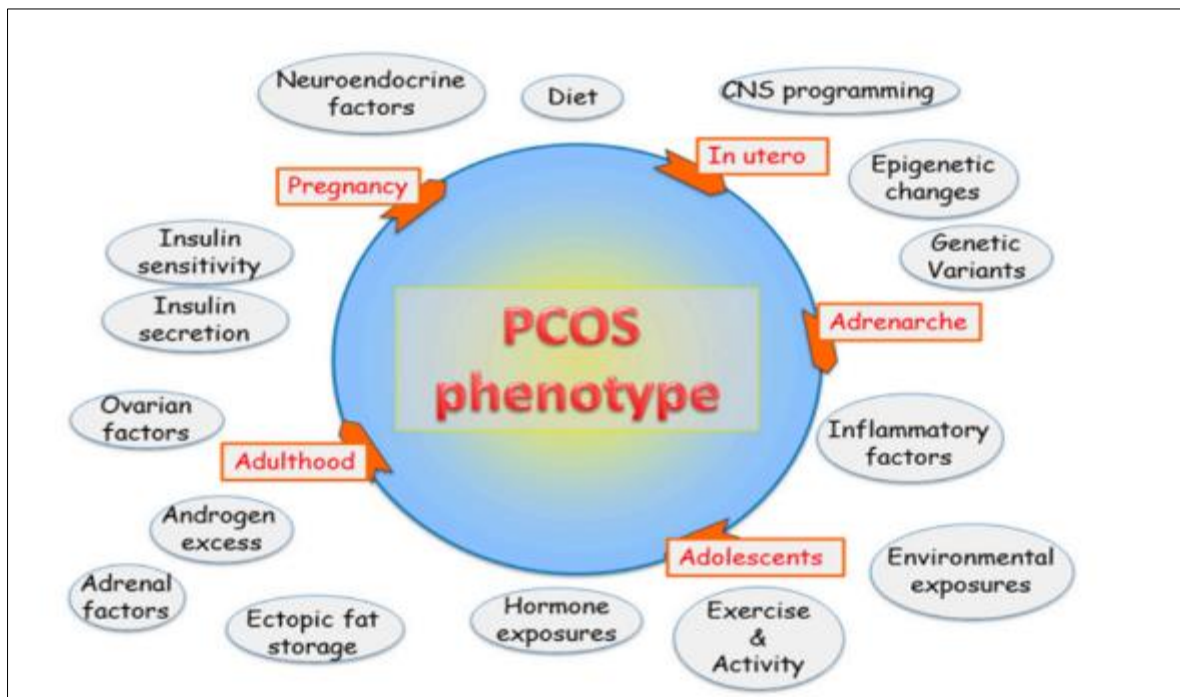


Figure 4 PCOS phenotypes

Excessive ovarian and/or adrenal androgen production is a hallmark of PCOS. The increased synthesis of ovarian androgen is caused by both internal ovarian causes such as altered steroidogenesis and external ovarian factors like hyperinsulinemia. In contrast to normal controls, women with PCOS have more developing follicles and early growth arrest of antral follicles at 5 to 8 mm. The string-of-pearl shape and theca interstitial hyperplasia, which are the hallmarks of the classic ovarian phenotype and reflect testosterone exposure, have also been seen in females with congenital adrenal hyperplasia (CAH) and in transgender people who are transitioning from female to male. Ovarian dysregulation in PCOS may be a result of distorted interactions between the endocrine, paracrine, and autocrine systems involved for follicular maturation. A quick summary of the follicular maturation stages is provided. Primordial follicles form during gestation and are made up of meiotically arrested oocytes that are encircled by pre-granulosa cells. As a result, throughout pregnancy, a woman's ovaries were exposed to the ambient maternal environment. Up until the start of puberty, ovaries are comparatively dormant [11]. There is a paucity of comprehensive research regarding the follicular morphology in prepubertal and early pubertal ovaries. Prepubescent and early pubertal girls' ovarian tissue

differs in follicle form and development capacity. Particularly, compared to pubertal ovaries, prepubertal ovaries have a higher percentage of dysfunctional, non-growing follicles. This finding's physiologic significance is not entirely known. Uncertainty surrounds the specific signalling processes that start follicular activation. The decision to continue in a resting state or to get active is likely influenced by a combination of variables. Follicle density appears to be one such influence. Up until the antral stage, early follicular development is gonadotropin-independent after activation from the resting pool. Granulosa cell-secreted anti-Mullerian hormone (AMH) limits initial follicular recruitment and signals follicular reserve. AMH appears to encourage preantral follicle growth to the antral stage in nonhuman primate (NHP) ovaries, in contrast to mice where AMH suppresses preantral follicle growth and antral follicle maturation. Antral follicles contain peak AMH contents. Oestradiol decreases AMH expression once FSH-stimulated granulosa cell concentrations reach the required threshold. follicular development in the ovary. The growth of ovarian follicles is depicted here during developmental stages [2]

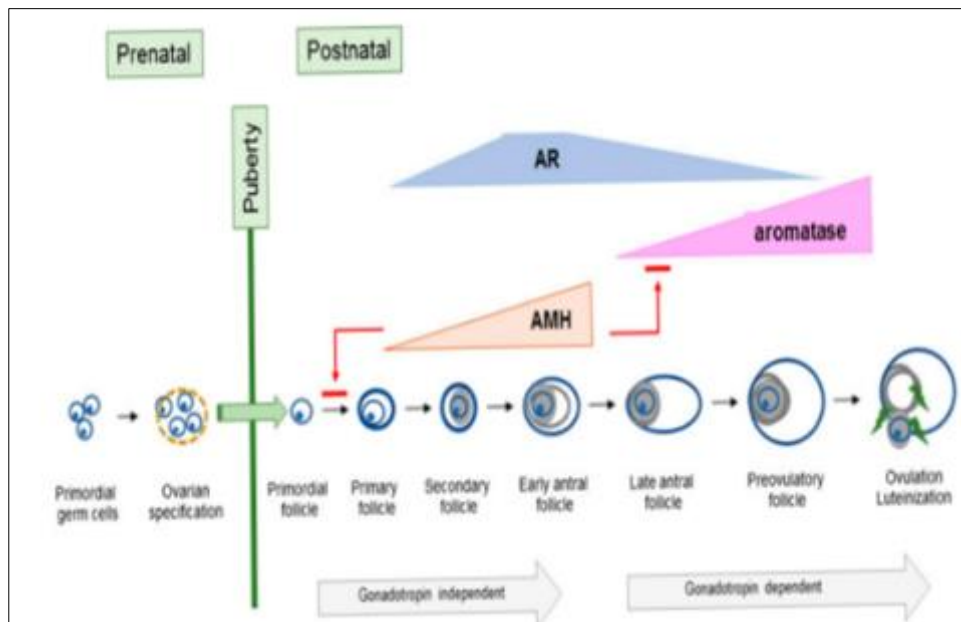


Figure 5 Rise of menstrual cycle

3.2. Complications:

In the past, the menstrual cycle and a woman's fertility have been the main concerns with Polycystic Ovary Syndrome (PCOS). But PCOS is a complicated condition that can affect numerous organ systems. PCOS can cause major long-term problems such as endometrial cancer, heart disease, diabetes, and metabolic syndrome if it is not properly handled. Despite the elevated risks for problems associated with PCOS, they can be avoided. Making long-lasting improvements to your diet and exercise routines should be your top priority[4].

4. Endometrial cancer

Compared to women without PCOS, those who have PCOS do have a slightly increased risk of acquiring endometrial cancer. A woman's risk increases when her periods become less regular and less frequent. The endometrium is exposed to hormones like oestrogen throughout a typical menstrual cycle, which causes the lining to multiply and thicken. Ovulation failure, which is common in PCOS, prevents the lining from being shed and exposes it to much greater levels of oestrogen, which causes the endometrium to thicken much more than it should. This is what makes it more likely for cancer cells to start growing. An essential component of controlling PCOS is restoring hormone balance in order to establish a regular menstrual cycle. Weight loss, exercise, and a balanced diet are crucial. In addition to oral contraceptives, metformin and inositol may help some PCOS-affected women have more regular menstrual cycles[5,9].

4.1. Early & Recurrent pregnancy loss

EPL is a concern for women who have pregnancy-related symptoms of polycystic ovarian syndrome. Clinical studies have shown that women with PCOS have a first-trimester miscarriage risk that is 50% greater than that of women without PCOS. Ovulation-inducing drugs used to treat polycystic ovarian syndrome pregnancy have greater incidence of EPL than those used in naturally conceiving women[1].

4.2. Androgens and EPL

According to two separate studies, one of the main reasons of EPL in PCOS women is an increase in the testosterone ratios and isolated elevations in free and total testosterone levels.

EPL is linked to insulin resistance and hyperinsulinemia in women with problems from polycystic ovarian syndrome.

4.3. Endometrial Dysfunction and Early Pregnancy Loss

Proteins secreted by the inner layer of the uterus/womb, known as the endometrium, are essential for the development of the fertilised egg and the preservation of pregnancy. These proteins exhibit a substantial connection with EPL in women with PCOS who also have loss of or abnormally low amounts of these proteins [2,8].

Negative pregnancy and birth outcomes are very likely in PCOS-positive women. This may call for a watchful attitude and close supervision from the first sign of pregnancy till delivery.

4.4. Recurrent pregnancy loss (RPL)

Described as two or more pregnancies lost in a row before the 20th week. This unpleasant incident strikes women with PCOS quite frequently.

4.5. PCOS & Hormonal Imbalance

Women who have PCOS, a hormonal condition that affects the way their ovaries and reproductive organs work, will have cysts in their ovaries. Between the ages of 15 and 44, when women are capable of having children, is when they can get this disorder. Because not all women with PCOS have ovarian cysts, the label may be misleading. But when they do, these cysts appear as tiny, fluid-filled sacs that develop inside the ovaries. One immature egg that did not trigger during the ovulation cycle is truly present in each cyst. The imbalanced hormone production is then brought on by the irregular ovulation.

There are numerous different symptoms, and many people with PCOS are completely unaware of it. However, PCOS can be associated with irregular or heavy menstrual periods, high levels of androgen, or male sex hormone, and infertility. Additional symptoms and indicators may include...

- Excess hair growth
- Weight gain
- Mood swings
- Pelvic pain
- Hair thinning
- Acne or oily skin
- Headaches
- Darkened skin on the neck or armpits

The risk of additional health issues like diabetes, heart disease, and high cholesterol may also increase if you have PCOS.

Although the exact reason of PCOS development is uncertain, researchers think that it is hereditary. Hormonal imbalance, inflammation, and elevated insulin levels can all contribute to PCOS development. The hormone insulin regulates the body's sugar levels. Insulin resistance is common in women with PCOS, which causes the body to create more of the hormone and interferes with ovulation. The increased production of hormones, such as testosterone, is a result of this process [13].

PCOS can also cause low levels of the hormone progesterone. This may prevent a woman from having menstrual cycles for a long time or make it difficult for her to predict when they will occur.

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Figure 6 PCOS & Hormonal Imbalance

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5. Diagnosis criteria

If other uncommon causes of the same symptoms have been ruled out and you satisfy at least two of the following three requirements, PCOS can typically be diagnosed.

- Periods – this indicates that your ovaries do not regularly release eggs (ovulate)
- Blood tests showing you have high levels of "male hormones", such as testosterone (or sometimes just the signs of excess male hormones, even if the blood test is normal)
- Scans showing you have polycystic ovaries
- The polycystic ovary syndrome (pcos) is the commonest endocrine disorder of reproductive-aged women with a prevalence of approximately 5% to 8%.[\[r hart, da doherty, t mori, rc huang, rj norman\]](#)

You won't absolutely need to have an ultrasound scan before the diagnosis of PCOS can be made because only two of these must be present.

National Institutes of Health Criteria (NIH), developed in 1990, only need the presence of clinical and/or biochemical hyperandrogenism and oligo/amenorrhea anovulation as diagnostic criteria for PCOS (Zawadski and Dunaif, 1992). Later in 2003, the Rotterdam Criteria added a third criterion to the two NIH criteria by using the ultrasound appearance of polycystic ovarian tissue. The diagnosis of PCOS was expanded by the Rotterdam consensus of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM), which required two of the three features of anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) as seen on ultrasound. Lastly, the Androgen Excess Society classified PCOS as hyperandrogenism with polycystic ovaries or ovarian dysfunction (Azziz et al., 2006). The Androgen Excess Society (AES) stated that androgen excess should be present and accompanied by oligomenorrhea or PCOM or both of them in order to confirm that androgen excess is a fundamental event in the development and pathogenesis of polycystic ovarian syndrome (Azziz et al., 2006) [3,7].

6. Prevention and Potential Cure of PCOS

Instead of concentrating on the underlying cause, the typical method to treating PCOS focuses on utilising drugs to alleviate symptoms. Taking birth control pills for irregular periods, as an illustration, or taking drugs for hirsutism and acne.

6.1. Beat Insulin Resistance

Understand and eliminate insulin resistance if you want to treat PCOS at its source. The good news is that lifestyle modifications can completely reverse insulin resistance in the majority of cases. In my book, I feature a case study of a lady who overcame PCOS and regained her fertility by making lifestyle adjustments.

7. Correct Key Micronutrient Deficiencies

Remember, even if you follow a low-fat, low-carb, low-calorie, vegan or vegetarian diet, you could still have serious micronutrient deficiencies that increase your risk of developing PCOS. Below are a few of the most significant ones:

7.1. B-vitamin deficiencies

B12 deficiency is associated with insulin resistance and, in pregnant women, can raise the baby's chance of developing type 2 diabetes. B12 insufficiency can also be caused by prolonged use of common PCOS drugs like metformin and oral contraceptives. Check your B12 levels with your doctor, make sure to eat foods high in B12, and think about taking supplements under your doctor's guidance.

7.2. Magnesium deficiency

A diet high in magnesium can help lower insulin resistance and treat various PCOS symptoms like PMS, headaches, mood problems, and exhaustion. Spinach, Swiss chard, pumpkin seeds, almonds, dark chocolate (70% plus in moderation), avocados, and other foods high in magnesium are just a few examples.

- **Zinc deficiency:** associated with low androgens and acne. Eat zinc-rich foods like nuts, seeds (pumpkin, sesame), certain meats (grass-fed lamb and beef in moderation), beans (garbanzos in moderation), unsweetened kefir/yogurt, spinach, etc.
 - **Vitamin D deficiency:** Deficient vitamin D is associated with insulin resistance and is commonly low in PCOS. Read my post on vitamin D.
 - **Iron deficiency:** Iron deficiency is often a consequence of PCOS, especially if women have heavy or prolonged periods. Iron deficiency in turn can make symptoms of PCOS worse like fatigue and mood disorders. Talk to your doctor to see if iron levels need to be checked and eat an iron-rich diet [14].
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8. Eliminate Toxin Exposures

Numerous pollutants that we are exposed to can disrupt hormonal balance and raise the risk of diseases like PCOS. Endocrine disrupting chemicals, or EDCs, are toxins that interfere with hormone function, and the most extensively researched ones are found in plastics like bisphenol A. (aka BPA). Some suggestions for minimising exposure:

- Switch to glass and stainless steel water bottles and food containers in place of plastic ones.
- Examine all household products, cosmetics for the skin, and other items, and choose "green" alternatives.
- Consume a diet that is as pure and natural as possible, including purified water.

Chronic stress and insulin resistance are two of the main underlying causes of micronutrient deficiencies. I observe the intense pressure parents put on their kids to perform at the highest level here in Silicon Valley. I've previously spoken and blogged about this subject. We are endangering our kids if this pressure is coming at the expense of a healthy diet, regular exercise, and enough rest and sleep. Just know that if you are the parent of a daughter, Type A parenting, which results in nearly all of the risk variables we've mentioned thus far[2,14], is a key trigger to PCOS.

9. Consider Cutting Back or Eliminating Dairy

Carry a larger risk than full fat milk. Dairy consumption might worsen some symptoms, such as acne, and increase testosterone production. Women should avoid dairy for 3–4 weeks, then reintroduce it to observe if their symptoms worsen. Frequently, during this time, acne entirely disappears. Some women find that completely cutting off dairy is beneficial, however others find that lowering their dairy intake to no more than 2 servings per day and putting an emphasis on fermented dairy (kefir, yoghurt) and high quality grass-fed full-fat dairy is sufficient[6].

10. Eat More Omega-3s

More Omega-3 fatty acids can lower androgens whereas excessive dairy consumption can enhance them. Consume foods high in these beneficial fats, such as egg yolks, nuts, seeds, and cold water fish (such as salmon, mackerel, albacore tuna, and sardines).

11. Increase Physical Activity

Maintaining a healthy amount of physical activity is necessary to prevent insulin resistance and maintain low blood sugar and insulin levels. Exercise is crucial, but food is also very important. I treat a lot of female patients who have always been physically active but have developed insulin-resistant diseases like type 2 diabetes and PCOS as a result of poor eating habits.

12. PCOS treatment

Treatments can help you control PCOS symptoms and reduce your risk of developing long-term health issues including diabetes and heart disease.

12.1. Metformin {Fortamet}

This drug lowers insulin levels. It can help with weight loss and may prevent you from getting type 2 diabetes.

Your doctor might advise weight loss surgery if you are really fat and other procedures haven't helped you lose weight. Your menstrual cycle and hormones may vary as a result, which may reduce your risk of developing diabetes.

12.2. Glycolipid Metabolism Index

Before and five menstrual cycles into the treatment, the two groups' indices of lipid and glucose metabolism were compared. An automatic biochemical analyzer was used to measure the changes in triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL) levels. The enzyme-linked immunosorbent assay was used to measure the levels of fasting insulin, HbA1c, and the insulin resistance index (HOMA-IR) (ELISA).

12.3. Spironolactone (Aldactone)

Your doctor might recommend this medication if birth control doesn't reduce hair growth after six months. Androgens, a particular class of sex hormone, are reduced by it. However, as it can result in birth malformations, you shouldn't take it if you're pregnant or intend to become pregnant.

The most popular fertility medication, Clomid (clomiphene citrate), is more effective for some women with PCOS than for others.

12.4. Prescription creams.

There are also treatments for hair issues that more directly target the skin or hair. These include prescription acne medications, cosmetic procedures including laser therapy and electrolysis, and the lotion eflornithine hydrochloride (Vaniqa).

12.5. Dexamethasone

My patients take this steroid medicine to aid with ovulation. I use it to avoid the disappointment of showing up for the follicle check and seeing that there aren't any follicles present, or at least none that are dominant. Because it can make you jittery, I advise my patients to take it first thing in the morning. On the first day of their cycle while taking Clomid/Femara, I have my patients take this. When they are ready to ovulate, I ask that they stop taking it. Ask your doctor if you can take this along with Clomid or Femara. It has been of great assistance to my PCOS patients[15].

- **Avandia (rosiglitazone)**, an oral drug of the same class as pioglitazone
- **Avandamet**, a combination of rosiglitazone and metformin
- **Victoza (liraglutide)**, an injectable drug used to control insulin and glucose levels

13. Age wise distribution in PCOS

Currently, around 22.5% of women, or one in five Indian women, have PCOS.

One in five Indian women have PCOS, which has become a major reason for concern. A significant 25% of Indian women were unaware of PCOS or PCOD, and 65% of women were unaware of PCOS symptoms, according to a poll of 2800 respondents across India[9].

Table 1 Percentile distribution of PCOS Women as per their Age

Age (years)	No of women with PCOS	Percentage %
15-24	50	5.0%
25-34	48	4.8%
35-44	2	0.2%
45-54	0	0%
55-64	0	0%
Total	90	10%

14. Conclusion

PCOS is an important condition that affects 6–10% of female births. Obese women had a considerably higher chance of developing PCOS. It accounts for 6% to 12% of female infertility cases globally, making it the most prevalent cause. It affects 3.7% to 22.5% of women in India.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest in publishing the paper.

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