Current Perspectives on the Genetic Basis of Polycystic Ovary Syndrome (PCOS)

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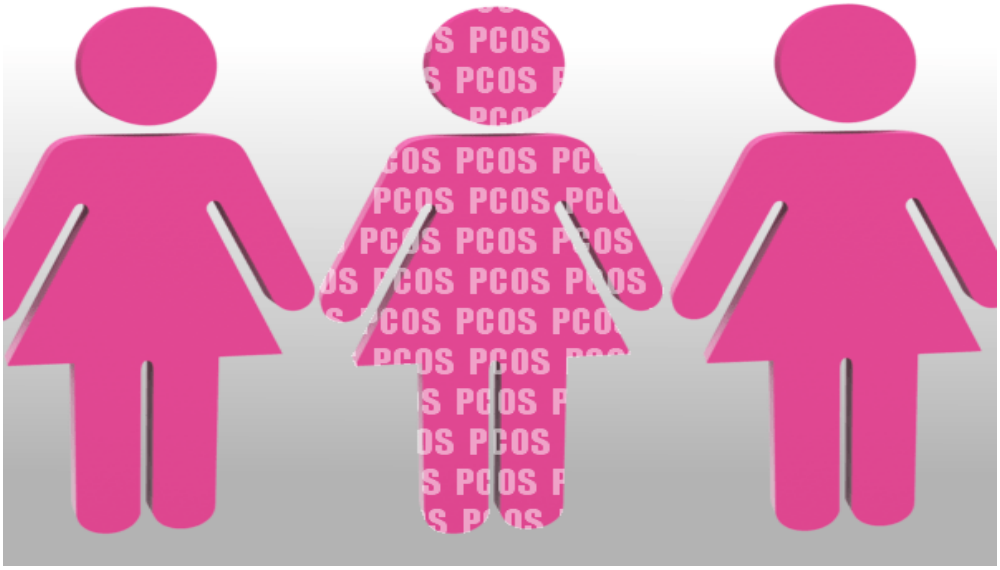
Key Points
➢ PCOS is a prevalent endocrine condition affecting females. ➢ In adolescents, PCOS presents with a mix of menstrual abnormalities and hyperandrogenism.



PCOS is a prevalent endocrine condition that affects females, particularly those who are of reproductive age. The prevalence of PCOS is thought to be between 5 and 10 percent worldwide.[1] Infertility, acne, amenorrhea or oligomenorrhea, hirsutism, insulin resistance, obesity, hyperandrogenism, and polycystic ovaries can all be seen by ultrasound as signs of PCOS. [2,3] There is strong evidence linking PCOS to infertility, which is thought to account for 40% of female infertility.[4] In addition, it is a major contributor to endometrial cancer.[2] PCOS is significantly linked to a variety of metabolic conditions, including hepatic steatosis, glucose intolerance, dyslipidemia, diabetes mellitus type II (T2DM), and hypertension, in addition to reproductive problems.

In the adolescent population, polycystic ovarian syndrome (PCOS) frequently presents with a mix of menstrual abnormalities and hyperandrogenism. Derangements in the balance of the pro- and antioxidant systems, androgen synthesis and action, relative gonadotropin ratios, ovulatory function, and insulin secretion and action are all linked to it.[5] The metabolic and reproductive effects of PCOS have been widely studied throughout life and constitute a lifelong condition. Insulin resistance is exacerbated in women with PCOS because they are typically overweight, often with significant abdominal or central obesity. These women are more likely to experience metabolic syndrome in later life, as well as impaired glucose tolerance (IGT), type 2 diabetes (T2DM), dyslipidemia, cardiovascular disorders, and hypertension.[6]

Studies have shown that in addition to physical illnesses, women with PCOS frequently display signs of poor self-esteem, despair, and impaired quality of

life.[7] PCOS is a complex illness, and it has been shown that certain genes, gene-gene interactions, or interactions between genes and the environment might affect a person's propensity to develop PCOS. Although genetic susceptibility has been linked to PCOS development in the past, there hasn't been agreement on an established genetic marker for the condition. Delineating the genetic architecture of this multifactorial condition involves finding causative variations in genes that may change its expression or ensuing protein function.[8] According to reports, phenotypic plasticity is caused by tissue-specific epigenetic changes that do not disrupt the genetic code and are mostly accomplished through mechanisms involving addition or reduction of chemical bonds in chromatin.[9,10]

To establish a PCOS diagnosis, prolonged anovulation and hyperandrogenism are necessary. The diagnostic criteria for PCOS have recently been expanded, and four additional clinical features have been added. The meaning of PCOS was widened by this.[11,12]

PCOS inheritance

Many people all over the world are affected by the multifactorial condition known as polycystic ovarian syndrome. Due to the numerous social and stress-related problems that people with PCOS experience, different facets of the condition were investigated in order to draw a firm conclusion. Infertile women with small, glossy ovaries were first discovered in 1972.[13] A second investigation into the deteriorating ovaries was published in 1844.[14] Research on several facets of PCOS, including its cellular mechanism, hormonal involvement, environmental risk factors, and genetic predispositions, continued. Cooper and colleagues published the first study on the genetic basis of PCOS in 1968.

Prevalence and Incidence

The National Institutes of Health (NIH) established criteria for PCOS diagnosis in 1990, and the calculation of PCOS prevalence depended on how many of the criteria were met. In various groups, especially Caucasians and Black people, the prevalence of PCOS was determined to be around 4% in each race. It was estimated to be 6.6 percent in both the black and white populations in a later study involving 400 women (aged 18 to 45), although there was a noticeable difference between white and black females, with rates of 8 percent and 4 percent, respectively. It was projected that 6.8% of Greek women sought assistance from free medical clinics. According to a study done on Caucasian Spanish people, the prevalence is 6.8%.[5]

A research at Oxford University and a private medical facility indicated that 6.8% of women had PCOS. Chinese women of reproductive age had a 5.6 percent prevalence of PCOS. Nearly all other populations share this prevalence. Nearly 9.13 percent of Indian women who are of reproductive age have PCOS. Compared to Caucasians, South Asians, particularly those in Pakistan, have a far greater frequency of PCOS. According to Rotterdam criterion 2003, Akram and Roohiet al. (2015) observed a greater prevalence of PCOS (50%). In a similar vein, Zahida et al. (2010) found that in Karachi, Pakistan, 40% of infertile women seeking medical treatment had PCOS.[6]

Clinical details of PCOS

The condition affects ovaries and causes many cysts, as the name suggests. In addition to an irregular menstrual cycle, many ovarian cysts, amenorrhea, and hirsutism in adult females, it is brought on by a hormonal imbalance. A multifactorial illness called PCOS primarily results in infertility, which upsets society.[5]

The patient with PCOS has high amounts of androgen, which results in subcellular abnormalities in the theca cells. Due to theca cell steroidogenesis' intrinsic activation in PCOS patients' theca cells—which occurs in the absence of trophic factors—a high quantity of androgen is released. This intrinsic activation also affects the granulosa cells, which results in higher blood levels of anti-mullerian hormone in PCOS patients compared to healthy women.[7]

The intrinsic aberration in PCOS is also responsible for the malfunction in the insulin signalling system, which is unrelated to obesity. Similar to this, PCOS

has also been linked to changes in the insulin gene expression pathway. Another glyco-oxidative stress mechanism has been identified as the pathophysiology driving PCOS. Oxidative stress can also produce insulin resistance, which in turn leads to hypergonadism. [4]

As its name suggests, PCOS is a complicated illness with a syndromic pathogenesis. The illness has several causes and frequently exhibits a range of symptoms. The four phenotypes of the illness are explained below.

Phenotype-Based Classification

Phenotypes A, B, C, and D are the four types of phenotypes that can be seen in PCOS.[2] Hyperandrogenism (HA), body mass index (BMI), and the severity of monthly irregularity all seem to be independent indicators of metabolic dysfunction, although ovarian shape does not seem to be. PCOS is divided into four phenotypes, including:

- By ultrasonography, oligoanovulation a large number of polycystic ovaries and hyperandrogenism.
- By ultrasonography, oligoanovulation, hyperandrogenism, and ovaries that seem normally.
- By ultrasonography, hyperandrogenism and polycystic ovaries with regular menstrual cycles were discovered.
- By ultrasound, polycystic ovaries, oligoanovulation and no hyperandrogenism were observed.

A and B PCOS phenotypes

Classic PCOS refers to the phenotypes A and B of PCOS. Women who exhibit more severe menstrual disruption, higher insulin production, increased insulin resistance, and increased risk for metabolic syndrome are said to have the typical PCOS phenotypes A and B. Compared to other PCOS phenotypes, the prevalence of obesity and atherogenic dyslipidemia (AD) is higher in classic PCOS. In contrast to healthy, normal controls and other PCOS phenotypes with normal androgen, hepatic steatosis is also more frequent in PCOS phenotypes A and B. The anti-mullerian hormone level is also markedly raised in individuals with traditional PCOS.

PCOS with ovulatory phenotype C

In contrast to individuals with classic and non-hyperandrogenic PCOS, those with phenotypic C (ovulatory PCOS) frequently have mildly raised blood insulin, atherogenic lipids, and androgen levels as well as high hirsutism ratings. Compared to other kinds of PCOS, metabolic disorders are also frequent in ovulatory PCOS. Higher socioeconomic class people were shown to have the ovulatory phenotype in an Italian sample of PCOS patients. The differences in ovulation patterns in high socioeconomic groups may be partially explained by differences in insulin levels and tissue fat distribution.

Nonhyperandrogenic PCOS, phenotype D

In compared to healthy controls, phenotypic D has the least metabolic dysfunction and normal testosterone levels, along with slightly raised levels of other endocrine substances.

Comparatively to those with typical PCOS, the endocrine finding includes higher levels of sex hormone-binding globulin, lower levels of T3 and T4, and a lower LH/FSH ratio. 49 Menstrual periods are mostly regular for those with PCOS phenotypic D, with sporadic aberrations.

Differences Related to PCOS

A multitude of anomalies contribute to PCOS, a complex condition. PCOS is linked to all genes and mutations that directly or indirectly impact the ovaries.

Treatment Status Currently

Although PCOS cannot be cured, there are therapy options to help women who are trying to get pregnant. The available therapies are emphasised in Figure 1.

Dietary Treatment

30% of PCOS patients have been reported to be obese. Dietary therapy are also thought to be effective in treating PCOS symptoms such irregular periods, insulin resistance, and irregular menstrual cycles. Bariatric surgery has been adopted to obtain

more hopeful outcomes because dietary habits and exercise do not demonstrate long-term effects.

Pills for oral contraception (OCPs)

OCPs, or combined oral contraceptives, are seen to be the preferred method of treating PCOS. Numerous endocrine problems, such as hirsutism and acne, are controlled by these medications. Due to the minimal risk of endometrial cancer, OCPs are safer than alternative treatments. The OCPs contain a progestogen-estrogen mixture that raises SHBG, which lowers LH and FSH, which lowers free T and ovarian androgen production.

Surgical Ovarian Perforation (LOD)

Other ovulation techniques are utilized when clomiphene citrate medication is unsuccessful in causing ovulation. In 1984, LOD was utilized for ovulation after ovarian wedge resection surgery was unsuccessful. LOD enhances ovarian androgen production, reduces insulin resistance, and raises SHBG levels. It is effective in 84 percent of patients. With LOD, fewer miscarriages have been documented. Women receiving LOD are evaluated by the serum anti-mullerian hormone (AMH) level. To further evaluate the effectiveness of LOD, additional research is needed.

Reproductive technology with assistance (ART)

Patients with PCOS can manage their infertility using a variety of techniques. The most popular treatment is ART. Exogenous gonadotropin is used in this procedure to stimulate the ovaries and cause them to release many follicles.

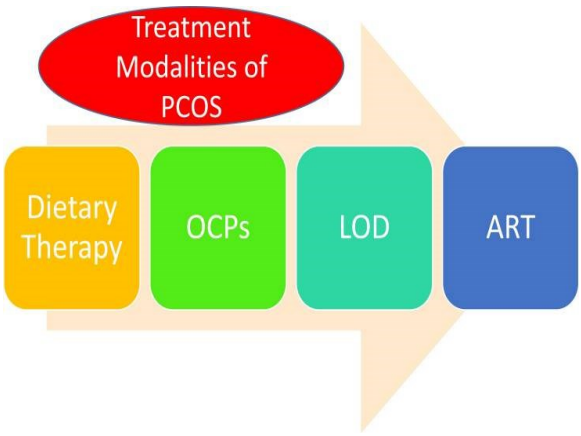


Figure 1: *Treatment of PCOS*[14]

Conclusion

COPs are being utilized as the first-line therapy for PCOS. These include a variety of ovulation-inducing medications. The related pathology is treated with several medications in combination, which improves the likelihood of pregnancy. However, these medications' side effects set off a variety of diseases, including heart pathology, diabetes mellitus, and depression.

Interventional techniques were used to lower the risk of related diseases. IVF, IVM fertilization, and laparoscopic drilling are some of these methods. Several secondary illnesses are present in conjunction with these operations. Given that PCOS has a complex pathophysiology and is difficult to treat, it is currently recommended that these patients be cared for by a team that includes an endocrinologist, a doctor, a gynaecologist, and a reproductive medicine expert.

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