Genetic Basis of Polycystic Ovary Syndrome (PCOS): Current Perspectives

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Abstract: Polycystic ovary syndrome (PCOS) is a common infertility disorder affecting a significant proportion of the global population. It is the main cause of anovulatory infertility in women and is the most common endocrinopathy affecting reproductive-aged women, with a prevalence of 8–13% depending on the criteria used and population studied. The disease is multifactorial and complex and, therefore, often difficult to diagnose due to overlapping symptoms. Multiple etiological factors have been implicated in PCOS. Due to the complex pathophysiology involving multiple pathways and proteins, single genetic diagnostic tests cannot be determined. Progress has been achieved in the management and diagnosis of PCOS; however, not much is known about the molecular players and signaling pathways underlying it. Conclusively PCOS is a polygenic and multifactorial syndromic disorder. Many genes have been associated with PCOS, which affect fertility either directly or indirectly. However, studies conducted on PCOS patients from multiple families failed to find a fully penetrant variant(s). The present study was designed to review the current genetic understanding of the disease. In the present review, we have discussed the clinical spectrum, the genetics, and the variants identified as being associated with PCOS. The mechanisms by which variants in the genes confer risk to PCOS and the nature of the physical and genetic interaction between the genetic elements underlying PCOS remain to be determined. Elucidation of genetic players and cellular pathways underlying PCOS will certainly increase our understanding of the pathophysiology of this syndrome. The study also discusses the current status of the treatment modalities for PCOS, which is important to find new ways of treatment.

Keywords: PCOS, infertility, genetics, treatment

Introduction
Polycystic ovary syndrome (PCOS) is a common endocrine disorder in females, especially in women of reproductive age. The worldwide prevalence of PCOS is estimated to be 5–10%1. PCOS could be diagnosed by infertility, acne, amenorrhea or oligomenorrhea, hirsutism, insulin resistance, obesity, hyperandrogenism, and polycystic ovaries by ultrasonography.2,3 Association of PCOS with infertility is well studied and is thought to be responsible for 40% of female infertility.4 Moreover, it is a leading cause of endometrial carcinoma.2 Besides reproductive abnormalities, PCOS is also strongly associated with a wide range of metabolic disorders, such as hepatic steatosis, glucose intolerance, dyslipidemia, diabetes mellitus type II (T2DM), and hypertension.5

Polycystic ovary syndrome (PCOS) typically manifests with a combination of menstrual dysfunction and hyperandrogenism in the adolescent population. It is...
The prevalence of PCOS in women is a multifactorial disorder where hormonal imbalance, relative gonadotropin ratios, ovulatory function, and balance of pro- and antiandrogen systems play a crucial role. PCOS is a lifelong disorder and the metabolic and reproductive ramifications of this syndrome are well documented in all stages of life. Women with PCOS are frequently obese with distinct abdominal or central obesity, which in turn aggravates insulin resistance. These women are at a higher risk of developing impaired glucose tolerance (IGT), T2DM, dyslipidemia, cardiovascular diseases, hypertension, and ultimately manifesting metabolic syndrome in their later lives. Apart from physiological maladies, studies have suggested that women with PCOS often show symptoms of negative body image perception, low self-esteem, depression, and decreased quality of life. PCOS is a multifactorial disorder where individual genes, gene–gene interaction, or gene–environment interactions have been reported to influence predisposition to PCOS development. Previously, the literature has reported the importance of genetic predisposition to PCOS development; however, no consensus has been reached on an established genetic marker for PCOS. Identifying causal variants in genes that may alter its expression or subsequent protein function helps to delineate the genetic architecture of this multifactorial disorder. Tissue-specific epigenetic alterations that do not affect the genetic code have been reported to be responsible for phenotypic plasticity and are mainly achieved by mechanisms involving the addition or removal of chemical groups in chromatin. Further, proteome profiling of pathophysiologically relevant tissues helps to elucidate the dynamic changes in the cellular proteome. Exploring genetic and epigenetic patterns with their consequent impact on protein profiles has contributed toward biomarker discovery and unraveling the molecular pathophysiology of PCOS. Thus, employing a multipronged approach and harnessing cutting-edge technologies has yielded copious and comprehensive data, which in turn have expanded and shaped the current understanding of PCOS etiology. Insight into this condition as well its far-reaching consequences will provide both researchers and clinicians new avenues into understanding the association between the various facets of this syndrome and treating this hormonal imbalance successfully and restoring fertility. The presence of chronic anovulation and hyperandrogenism is required to establish a PCOS diagnosis. Recently, the diagnostic criteria have been extended and four clinical characteristics have been added to establish PCOS diagnosis. This expanded the definition of PCOS.

**Inheritance of PCOS**

Polycystic ovarian syndrome is a multifactorial disease affecting a significant number of people around the world. Individuals with PCOS face multiple social and stress-induced issues; therefore, various aspects of PCOS were studied to reach a definite conclusion. Historically, in 1972, infertile women with tiny, shiny ovaries were identified. Later, in 1844 another study on the degenerative ovaries was reported. Studies continued and different aspects such as cellular mechanism, hormonal involvement, environmental risk factors, and genetic determinants of PCOS were studied. The genetic basis of PCOS was first reported by Cooper and colleagues in 1968. Studies on PCOS reported multiple relatives and siblings in families with autosomal dominant inheritance. The prevalence of PCOS in the first-degree relative of the proband that was found in nearly 55–60% in several small families supported the hypothesis of autosomal dominant inheritance of PCOS. Later on, monogenic causes of hirsutism and oligomenorrhea in PCOS women and male-pattern baldness were identified.

Twin studies in small cohorts of mono- and dizygotic twin pairs suggested that PCOS is neither an autosomal dominant nor a monogenic disease; rather, it is an X-linked polygenic disorder. Moreover, twin studies estimated 72% variance in risk of PCOS to be genetic in basis, highlighting the genetic involvement.

**Incidence and Prevalence**

PCOS is diagnosed by criteria set by the National Institutes of Health (NIH) in 1990 and the estimation of the prevalence of PCOS depends on how many of the criteria were followed. The prevalence of PCOS was estimated in different populations, primarily in Caucasian and black races, and was estimated to be nearly 4.0% in both races. In a subsequent study involving 400 women (age range 18–45 years) it was estimated to be 6.6% in both black and white populations, while a significant difference was noted in white and black females, i.e., 8% and 4%, respectively. In Greek women, the prevalence estimated in females seeking help in free medical camps was 6.8%. A study conducted in Spanish Caucasians estimated the prevalence to be 6.8%. In a study conducted at Oxford University and a private medical center, a 6.8% prevalence of PCOS was estimated. The prevalence of PCOS in
Chinese women of reproductive age is 5.6\% \textsuperscript{24} This prevalence is nearly similar to the other populations. PCOS is also quite prevalent in Indian females of reproductive age, at nearly 9.13\%. \textsuperscript{25} The prevalence of PCOS is significantly higher in the South Asian population, especially in Pakistan, as compared to Caucasians. Akram and Roohiet \textit{et al.} \textsuperscript{(2015)} reported a higher prevalence of PCOS (~50\%) according to Rotterdam criteria \textsuperscript{2003}.\textsuperscript{26} Similarly, Zahida \textit{et al.} \textsuperscript{(2010)} reported a 40\% prevalence of PCOS among infertile women seeking medical advice in Karachi, Pakistan.\textsuperscript{27}

\textbf{Clinical Description of PCOS}

As the name indicates, the disease involves ovaries with many cysts. It is caused by a hormonal imbalance, which is further indicated by an irregular menstrual cycle, many cysts in the ovaries, amenorrhea, and hirsutism in adult females. PCOS is a multifactorial disease that primarily causes infertility and thus creates social imbalance.

Subcellular aberrations in theca cells are caused by elevated levels of androgen in the patient with PCOS. In theca cells of PCOS patients, a high level of androgen is secreted due to the intrinsic activation of theca cell steroidogenesis despite the absence of trophic factors.\textsuperscript{28} The granulosa cells are also affected by this intrinsic activation, which leads to elevated levels of serum anti-mullerian hormone in PCOS patients as compared to healthy women.\textsuperscript{29–31}

Elevated pre-antral and small antral numbers of follicles in PCOS have also been reported in multiple studies.\textsuperscript{32} In maturing follicles, a defective apoptotic process further increases the number of follicles in PCOS women.\textsuperscript{33}

The defect in the insulin signaling pathway independent of obesity is also due to intrinsic aberration in PCOS.\textsuperscript{34} Similarly, alteration in the insulin gene expression pathway has also been attributed to PCOS.\textsuperscript{35} Another pathway of glyco-oxidative stress has been reported as an underlying pathology of PCOS.\textsuperscript{36} Insulin resistance can also be elicited by oxidative stress, which further causes hypergonadism.\textsuperscript{37}

PCOS is a complex disease and syndromic in pathology as the name indicates. The disease is multifactorial and often of variable symptoms. The disease is grouped into four phenotypes as discussed below.

\textbf{Classification Based on Phenotype}

Four phenotypes can be observed in PCOS: phenotype A, phenotype B, phenotype C, and phenotype D. In general, it appears that the presence of hyperandrogenism (HA), body mass index (BMI),\textsuperscript{38} and degree of menstrual irregularity,\textsuperscript{39} but not ovarian morphology, is independent predictors of metabolic dysfunction. PCOS is classified into four phenotypes as:

(A) By ultrasound, numerous polycystic ovaries, oligoanovulation, and hyperandrogenism.
(B) By ultrasound, normal appearance of ovaries, oligoanovulation, and hyperandrogenism.
(C) By ultrasound, polycystic ovaries with normal routine menses and hyperandrogenism.
(D) By ultrasound, polycystic ovaries, oligoanovulation, without hyperandrogenism.

\textbf{PCOS Phenotypes A and B}

PCOS phenotypes A and B are termed classic PCOS. Women with the classic PCOS phenotypes A and B present with more significant menstrual dysfunction, increased secretion of insulin, increased insulin resistance, and increased risk for metabolic syndrome. A high incidence of obesity and atherogenic dyslipidemia (AD) is prevalent in classic PCOS as compared to other PCOS phenotypes.\textsuperscript{40} An increased risk of hepatic steatosis is also more common in PCOS phenotypes A and B in comparison with normal healthy controls and other phenotypes of PCOS with normal androgen.\textsuperscript{41} The classic PCOS is also characterized by a significantly elevated level of anti-mullerian hormone.\textsuperscript{42}

\textbf{Phenotype C – Ovulatory PCOS}

Mildly elevated serum insulin, atherogenic lipids, and androgen levels, and high hirsutism scores are common in phenotype C (ovulatory PCOS) patients in comparison to classic and non-hyperandrogenic PCOS. Metabolic syndromes are also common ovulatory PCOS as compared to other types.\textsuperscript{43} In an Italian cohort of PCOS patients, the ovulatory phenotype was reported among individuals with higher socioeconomic status.\textsuperscript{44} In high socioeconomic groups, tissue fat distribution and insulin level due to eating habits could partially explain the difference in ovulation patterns.

\textbf{Phenotype D – Nonhyperandrogenic PCOS}

The classical characteristics of phenotype D include normal androgen with slightly elevated other endocrine levels and the lowest metabolic dysfunction\textsuperscript{45,46} in comparison to healthy controls.\textsuperscript{47,48} The endocrine finding includes an
elevated level of sex hormone-binding globulin, a low level of T3 and T4 and a lower LH/FSH ratio in comparison to individuals with classic PCOS.\textsuperscript{49} Normally, individuals with PCOS phenotype D have regular menstrual cycles with intermittent irregularities.\textsuperscript{50}

In fact, PCOS is a complex and multifactorial disease and not all investigators agree with the classifications. In German PCOS patients presented with different PCOS phenotypes, no significant differences in insulin resistance, dyslipidemia, or BMI were observed.\textsuperscript{51} Similar nonsignificant differences among different PCOS phenotypes were also reported in Greek women with PCOS.\textsuperscript{52} In the Greek study, insulin resistance was observed in individuals with a BMI of more than 25 kg/m\textsuperscript{2}.\textsuperscript{52} Similarly, no significant variation in metabolic syndrome among women with PCOS from Sri Lanka and Brazil was reported.\textsuperscript{53,54} However, an elevated level of low-density lipoprotein (LDL) in ovulatory PCOS individuals from a nonhyperandrogenic Turkish PCOS cohort was reported,\textsuperscript{55} although the difference in androgen level could be attributed to the substandard estimation method of androgen, which leads to misclassification.\textsuperscript{56}

Different diagnostic criteria have been employed in categorizing PCOS. The NIH criteria accept only phenotypes A and B,\textsuperscript{11} the Rotterdam consensus recognized all four categories of phenotypes,\textsuperscript{57} whereas the AES-PCOS declared the phenotypic categories A, B, and C.\textsuperscript{58}

The most frequently identified phenotype is A, with 44–65%, followed by B with 8–33%, phenotype C with 3–29%, and D with 0–23%.\textsuperscript{43,48}

### Genetics of PCOS

PCOS is an extremely heterogenetic and complex disease. The genetic basis of PCOS is different between families and within families but is related to a common pathway. Due to complexity and heterogeneity single gene or related genes in a single family have not been reported.

The genetic susceptibility of different genes is different in patients from the same family.\textsuperscript{59} Recently, intrauterine programming as a susceptibility factor has been hypothesized for PCOS.\textsuperscript{60} Genome screening to search for a candidate gene in a complex disease like PCOS is unrealistic. Linkage analysis in such families always comes up with negative results. In such a disease, case-control studies of larger population size and genome-wide association studies (GWAS) are helpful to find possible associations. Parental analysis in such diseases is often impractical; however, known risk of disease can be estimated.\textsuperscript{61}

### Mutations

Many studies have been conducted in multiple families to find the causative gene/mutation, but no true penetrance of a single gene mutation has been reported until now. All genes/mutations reported in familial aggregation show low penetrance associated with other covariant, hormonal or environmental factors to cause disease. Conclusively, PCOS is a polygenic and multifactorial syndromic disorder.

### Variations Associated with PCOS

PCOS is a multifactorial disease and is caused by a number of abnormalities. All genes/mutations that affect ovaries directly or indirectly are associated with PCOS. An overview of the genetic picture of PCOS is depicted in Figure 1. These groups of related genes and their roles in PCOS are discussed below in detail.

### Genes Involved in Ovarian and Adrenal Steroidogenesis

The most common endocrine disorder associated with PCOS is an elevated androgen level. Hence, uncovering the reason for the elevated level of androgen, several genes have been reported to be associated with PCOS, as follows.

#### CYP11a

The gene \textit{CYP11a} encodes an enzyme that is required in an intermediary step of cholesterol conversion to progesterone. This is a rate-limiting step in the conversion of cholesterol.\textsuperscript{62} Further more, Gharani et al. reported polymorphs and variation as associated factors in a study of 97 infertile women.\textsuperscript{63} Two other studies from China and Greece replicated the finding and reported \textit{CYP11a} to be an association factor with PCOS.\textsuperscript{64,65} Later on, a large study conducted in the UK did not replicate the results.\textsuperscript{66}

#### CYP21

In the synthesis of steroid hormones, the conversion of 17-hydroxypregesterone to 11-deoxycortisol is catalyzed by an enzyme that is encoded by \textit{CYP21}. A less-active enzyme due to variation leads to ineffective anabolism of steroidogenesis, which further causes PCOS.\textsuperscript{67} Witchel et al. reported heterozygous \textit{CYP21} associated with PCOS-like disease with hyperandrogenemia.\textsuperscript{67} Direct association of \textit{CYP21} variation with PCOS failed in 114 women with PCOS.\textsuperscript{68}
CYP17
The conversion of pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone is catalyzed by an enzyme (P450c17α) that is encoded by CYP17. Rosenfield et al. reported elevated androgen levels in PCOS patients. Wickenheisser et al. reported increased expression of CYP17 in theca cells. Carey et al. reported a polymorph in the promoter region that is associated with PCOS.

CYP19
The CYP19 gene responsible for aromatase p450, necessary for the formation of estrogen, lies on chromosome number 15q21.2. Lower activity of aromatase activity is reported in both obese and lean women with PCOS.

Genes Involved in Steroid Hormone Effects
Androgen Receptor Gene
The “q” arm of chromosome X contains the AR gene, which is composed of 11 exons and encodes a 90-kb long tridomain protein. Mutations and structural disruption of the gene are reported to cause PCOS. “X” chromosome inactivation leads to disruption of the cellular pathway, causing elevated androgen hormone resulting in PCOS. As the AR gene is located on the X chromosome, a change in a single copy of the gene is sufficient to cause pathology. GWAS also reported a novel variation in the gene to be the cause of PCOS.

Sex Hormone-Binding Globulin Gene
The SHBG gene is localized to chromosome 17p13-p12. SHBG synthesizes a protein of 373 amino acids. The protein product of SHBG controls the level of sex hormones in the body by binding to androgens, predominantly with estrogens and testosterone. Most of the SHBG is synthesized by hepatocytes in the liver. SHBG synthesis by hepatocytes is controlled by multiple metabolic factors, such as androgens and insulin. Concentrations of SHBG are lower in females with PCOS, which has been mainly attributed to an inhibitory consequence of hyperinsulinemia on SHBG synthesis. Single nucleotide polymorphism in the SHBG gene was described to be significantly associated with PCOS in numerous studies.

Genes Involved in Gonadotropin Action and Regulation
Lutein Hormone (LH) and Its Receptor Gene
Both LH level and distorted function of LH are frequently reported as a cause of PCOS. These abnormalities cause annulations, thus producing PCOS. A high level of LH subsequently enhances the production of androgen. The negative feedback in response to elevated LH is reduced follicle-stimulating hormone
The gene encoding for both LH and its receptor has been studied in PCOS to find the possible association. Initially, a point mutation (Trp8Arg and I1g15Thr) in a gene encoding the B subunit was reported in patients with PCOS. The same mutation was reported to be nonpathogenic and is found in 15% of the normal population. Polymorphism in the LH β-subunit gene has also been reported to be associated with PCOS.

AMH
The AMH gene is located on the long arm of chromosome 19 at cytogenetic location 13.3. The gene consists of five exons and encodes a protein that is involved in infertility. Variation in the AMH gene is associated with PCOS. Whole exome-sequencing and GWAS reported several variants of the AMH gene as strong predictors of PCOS.

Follicular Stimulating Hormone Receptor (FSHR)
FSHR is located on the “p” arm of chromosome 2 and consists of 14 exons. The gene encodes a protein G-coupled receptor, which is required for gonad development. Mutation in the gene disrupts the structural protein, thus causing an imbalance of the hormone. Hormonal imbalance causes PCOS. A comparison of polymorphs in healthy and affected individuals in north Iraq showed a higher frequency of the gene among the affected individuals.

Genes Involved in Insulin Action and Secretion
The Insulin Gene
Insulin also plays a significant role in the production of androgen by receptors present on theca cells. This act of insulin is provoked through the pathway (phosphoinositide 3-kinase/protein kinase B), which becomes active in PCOS theca cells. Similar to LH, a high level of insulin also further enhances the synthesis of androgens. The INS gene is a sandwich gene at 11p15.5 between tyrosine hydroxylase and IGF-II. The 5′ untranslated region is occupied by a tandem repeat of VNTR. The transcriptional rate of INS and IGF-II is regulated by VNTR polymorphism. The number of repeats of VNTR ranges from 26 to 200. This VNTR polymorphism is associated with PCOS.

INSR
This gene encodes turmeric protein composed of two alphas and two beta chains. Several studies were conducted to find the association of infertility in obese women with PCOS, but they did not find any association. Conway et al. also studied the tyrosine kinase domain-encoding region of INSR in women with PCOS. Talbot et al. scanned the entire gene in women with PCOS. Neither of these studies found any association between PCOS and INSR. A larger part of chromosome 19p13.2 was searched and D19S884 was reported as the strongest association with PCOS. This region of the chromosome also contains the INSR gene.

Insulin Receptor Substrate Proteins
Insulin binds with its receptor. Activation of the receptor is autophosphorylated by the binding of insulin. Subsequently, the tyrosine kinase activity of INSR receptor phosphorylates IRS-1 and IRS-2. These activated substrates are then further utilized in the downstream process. Several studies have been performed to find out the association in the genes of IRS-1 and IRS-2 and PCOS. Petermann et al. reported a higher frequency of Arg972 IRS-1 in women with PCOS, while El Mkadem et al. reported no significant difference between the mentioned mutation in PCOS patients and controls. Dilek et al. reported a much higher frequency of Gly972Arg in IRS-1 in Turkish women with PCOS. Reports of both association and no association have been reported. These differences highlight environmental and ethnic involvement.

Calpain10 Gene
CAPN10 is located on the long arm of “q” of chromosome 2 and consists of 12 exons. The gene encodes calcium-dependent cysteine protease, which is a heterodimeric protein. The gene is associated with diabetes mellitus type 1. The protein “calpain 10” interferes with insulin metabolism and secretion. The impaired insulin level causes PCOS; thus, a mutation in calpain 10 also causes PCOS. Hence, CAPN10 is a candidate gene causing PCOS.

Other Genes
Fat Mass Obesity (FTO)
The FTO gene encodes an enzyme, alpha-ketoglutarate. The gene is located on the “q” arm of chromosome 16. The gene is reported as an association for obesity and T2DM.

In a study conducted in Pakistani women with PCOS, single nucleotide polymorphism (SNP) rs9939609 was significantly associated with diseases. The SNP rs9939609 was significantly higher in affected women as compared to healthy participants of the study.
PCOS1
The cytogenetic location of PCOS1 is 19p13.2. The gene has been associated with PCOS in several studies. The gene is also known as PCO and it is actually a susceptibility region on chromosome 19. Initially, it was identified in two sisters in 1971. Later on, the study was replicated in 2005 by Urbanek et al.\textsuperscript{112}

SRD5A2 and SRD5A1
The cytogenetic location of SRD5A2 is 2p23.1. Increased activity of SRD5A among women with PCOS as compared to normal females was reported in 1999 by Jakimiuk et al.\textsuperscript{113} Later in 2006, SRD5A2 and SRD5A1 were tested as susceptibility in hirsutism patients, and it was reported that a variant in SRD5A2 was associated with protection to PCOS while variants in SRD5A1 were associated with risk of hirsutism and thus PCOS.\textsuperscript{114}

Epigenetics of PCOS
Heritable changes in gene expression that are not due to a sequence change of DNA but that are transgenerationally and mitotically heritable are known as epigenetic changes. Epigenetic involvement of many diseases has been reported, such as T2DM,\textsuperscript{115} PCOS,\textsuperscript{116} and prostate cancer.\textsuperscript{117} Higher secretion of androgens in fetal life has been reported to cause diseases in rats,\textsuperscript{118} monkeys,\textsuperscript{119} and sheep models. The symptoms of diseases are similar to PCOS. Although it is ethically restricted to use humans for experimentation, certain studies have shown that an increased level of androgen during fetal life predisposes the offspring to PCOS-like symptoms in later stages.\textsuperscript{120} Qu et al. reported a differential CPG island methylation in PPARG1, NCOR1 of granulosa cells that causes hyperandrogenism-induced epigenetic alteration, and thus the development of ovarian dysfunction.\textsuperscript{121} Ning Xu et al. reported an altered DNA methylation pattern in PCOS patients as compared to control groups.\textsuperscript{116}

This epigenetic involvement of PCOS highlights the complexity of the disease.

Current State of Treatment
PCOS is not a curable disease; however, to assist females seeking conception, treatment modalities are available. The treatment options are highlighted in Figure 2 and are discussed in detail below.

Dietary Therapy
Obesity has been reported in 30% of PCOS patients. The symptoms of PCOS are also considered to be recovered by dietary therapies including resistance to insulin, annulations, and irregular menstrual cycle.\textsuperscript{122} However, dieting habit and exercise does not show long-term results; hence, bariatric surgery has been introduced to get more promising results.\textsuperscript{123}

Oral Contraceptive Pills (OCPs)
Combined oral contraceptive pills (OCPs) are considered the choice of treatment in treating PCOS. These drugs regulate multiple endocrine abnormalities including hirsutism and acne.\textsuperscript{124} OCPs are safer compared to other therapies because of the low risk of endometrial cancer.\textsuperscript{125} The OCPs include an amalgamation of progestogen and estrogen, which increases SHBG which decreases LH and FSH, which in turn decreases free T and ovarian androgen production.\textsuperscript{126} Hence, a low dose of progestogen is recommended in OCPs. Some adverse effects have also been reported with OCPs, i.e., hyperglycemia, impaired glucose metabolism, insulin resistance, and diabetes mellitus.\textsuperscript{127,128}

Laparoscopic Ovarian Drilling (LOD)
When clomiphene citrate therapy fails to produce ovulation, other methods of ovulation are used. LOD was used for ovulation in 1984 when ovarian wedge resection surgery failed. LOD is successful in 84% of patients and improves ovarian androgen production insulin resistance\textsuperscript{128} and increases the SHBG levels.\textsuperscript{129} Lower rates of miscarriages have been reported with LOD.\textsuperscript{130} Serum anti-mullerian hormone (AMH) level is used as an assessment tool for women treated with LOD.\textsuperscript{131} However, more studies are required to assess further the efficacy of LOD.

Figure 2 Summary of treatment modalities of PCOS.
Assisted Reproductive Technology (ART)
Several methods are used for the treatment of fertility in PCOS patients. ART is the most frequently used. In this method, the ovaries are stimulated with exogenous gonadotropin which produces multiple follicles. However, exogenous gonadotropin causes ovarian hyperstimulation syndrome (OHSS) in these patients. Due to the use of this treatment modality, in vitro maturation (IVM) is used. Many studies have been conducted to assess the efficacy of ART compared to traditional IVF techniques. Results are comparable in both traditional IVF and IVM-IVF.

Future Perspectives in the Treatment
Currently, COPs are used to treat PCOS as the first-line treatment. These include multiple medicines that increase ovulation. Combinations of medicines are used to treat the underlying associated pathology, which increases the chances of conception. However, the adverse effects of these medicines initiate multiple pathologies, such as cardiac pathology, diabetes mellitus, and depression.

To reduce the risk of associated pathologies, interventional procedures were adopted. These procedures include IVF, IVM fertilization, and laparoscopic drilling. These procedures are also accompanied by a number of secondary diseases.

Keeping in view the pathophysiology of PCOS as a multifactorial disease and the problems encountered in treating the disease, it is now suggested that a team composed of an endocrinologist, a physician, a gynecologist, and a reproductive medicine specialist will help these patients.

Author Contributions
Sulman Basit conceptualized the study idea and reviewed the manuscript; Anwar Ullah and Muhammad Jaseem Khan drafted the manuscript. All authors read and approved the final manuscript. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
The authors declare that they have no competing interests in this work.

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