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Beyond the Genome: Deciphering the Role of Key Genes in PCOS/PCOD: Current & Future Perspectives

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Abstract

Polycystic Ovary Syndrome (PCOS) is a complex gynaecological, metabolic, and endocrine disorder that affects women of reproductive age. Characterized by hyperandrogenism, menstrual irregularities, and multiple cysts in the ovaries, it has a significant genetic component. This review explores key genes implicated in the pathophysiology of PCOS, including those involved in steroidogenesis, insulin resistance, inflammation, and metabolic dysfunction. Genes such as CYP11A1 and CYP17 are linked to hyperandrogenism, while variations in FSHR and LH receptor genes contribute to ovulatory dysfunction and anovulation. Insulin resistance, a hallmark of PCOS, is influenced by mutations in genes like INSR, IRS1, and PPAR-γ, which affect insulin signalling and glucose metabolism. Additionally, genetic variations in FTO and MC4R are associated with obesity and metabolic syndrome in PCOS patients. It also involves chronic low-grade inflammation, with TNF-α and IL-6 genetic polymorphisms playing a role. Hormonal imbalances, including disrupted feedback loops between the hypothalamus, pituitary gland, and ovaries, are linked to genetic changes in GNRHR and FSHB. While mutations in BRCA1 and 2 and CYP11B2 are not directly associated with PCOS, they may influence related reproductive and metabolic processes. Current treatment options focus on lifestyle modifications, insulin sensitizers, and hormonal therapies, but future research aims to develop personalized treatments based on genetic findings, enhancing the management of PCOS and reducing long-term health risks.

Keywords: Polycystic Ovarian Syndrome; Hyperandrogenism; Anovulation; Obesity; Insulin Resistance

Abbreviations

PCOS: Polycystic Ovary Syndrome; PCOD: Polycystic Ovarian Disorder; WHO: World Health Organization; NIH: National Institutes of Health; GWAS: Genome-Wide Association Studies; FSHR: Follicle-Stimulating Hormone Receptor; LH: Luteinizing Hormone; INSR: Insulin Receptor; IRS1: Insulin Receptor Substrate 1; PPAR-γ: Peroxisome Proliferator Activated Receptor Gamma; MC4R: Melanocortin 4 Receptor; FTO: Fat Mass and Obesity-Associated Gene; TNF-α: Tumor Necrosis Factor Alpha; IL-6: Interleukin 6; GNRHR: Gonadotropin-Releasing Hormone Receptor; FSHB: Follicle Stimulating Hormone Beta-Subunit; SHBG: Sex Hormone Binding Globulin; BRCA1/2: Breast Cancer Genes 1 and

2; CYP11A1: Cytochrome P450, Family 11, Subfamily A, Member 1; CYP17: Cytochrome P450, Family 17; CYP11B2: Cytochrome P450, Family 11, Subfamily B, Member 2; CYP21: Cytochrome P450, Family 21; CAH: Congenital Adrenal Hyperplasia; ESHRE: European Society of Human Reproduction and Embryology; AE-PCOS: Androgen Excess and Polycystic Ovary Syndrome Society; ART: Assisted Reproductive Technology; IVF: In-Vitro Fertilization.

Introduction

PCOS (polycystic ovarian syndrome) also sometimes called Polycystic ovarian disorder (PCOD) is a gynaecological, metabolic and endocrine disorder affecting the reproductive aged women. It also has another name, known as Stein Leventhal syndrome. Although they sound similar, yet there is a minute difference between these two. In PCOD, immature eggs are released by the ovaries which causes hormonal changes leading to swollen ovaries while in the case of PCOS, ovaries tend to produce excess androgens due to endocrine dysfunction which makes the eggs turn into cysts [1]. Symptoms include hypergonadotropism, amenorrhea, oligomenorrhea, multiple cysts in ovaries, hirsutism, obesity, and commonly associated with infertility. It is also characterized by multiple metabolic abnormalities such as insulin resistance, high incidence of impaired glucose tolerance, endothelial dysfunction, hypertension, and dyslipidaemia resulting in an increased risk for diabetes and cardiovascular disease. The characteristics of PCOS are depicted in figure 1. Besides, there are a wide range of complications seen in pregnant women with polycystic ovaries like multiple pregnancy, stillbirth, hypertension induced in pregnancy period or pre-eclampsia, and gestational diabetes mellitus, small gestational age, and postpartum complications like postpartum depression, postpartum pre-eclampsia and post-partum cardiomyopathy [2,3]. According to World Health Organization (WHO), it has affected around 8-13% women worldwide. The prevalence of PCOS is highly variable globally, it ranges from 2.2% to 26%. According to NIH data, there is an increase in prevalence of disease from 6% to 9% and in India alone the range lies between 3.7% to 22.5% [4].

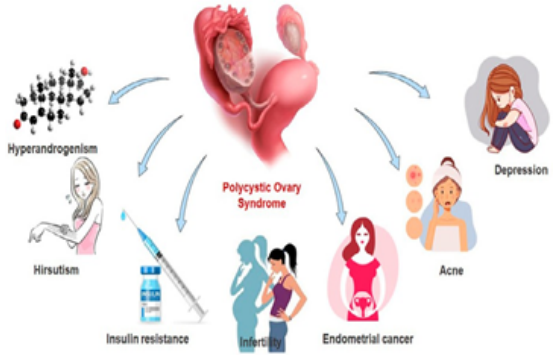

Figure 1: General Characteristics of PCOS.

Initially, in 1980s-1990s era, it was assumed that PCOS/PCOD is solely caused by dysregulated androgen secretion causing functional ovarian hyperandrogenism. Later studies showed that about two-thirds of cases fall under this category while in some cases the testosterone levels rise with reduced adrenal androgen production and few suffer from functional adrenal hyperandrogenism [5]. PCOS/PCOD is usually identified by irregular menstrual cycles, hyperandrogenism and ovarian morphology containing multiple cysts [6]. It not only limited to this but comes with other clinical implications such as skin hyperpigmentation, hirsutism, acne, alopecia and inflammatory reactions. The clinical signs and symptoms of PCOS along with their frequency of occurring are listed in Table 1.

Numerous risk factors, including environmental influences, genetic disorders like obesity, and endocrine dysfunctions leading to disrupted androgen and insulin levels, contribute to the development of PCOS [7]. This condition may cause significant issues, including infertility, miscarriage, diabetes, metabolic syndromes, and potentially ovarian cancer [8,9]. Therefore, accurate diagnosis and effective treatment are crucial in preventing the progression of PCOS to more severe stages.

Symptoms	Frequency
Oligomenorrhea	29-52%
Amenorrhoea	19-51%
Hirsutism	64-69%
Obesity	35-41%
Acne	27-35%
Alopecia	3-6%
Acanthosis nigricans	<1-3%
Infertility	20-74%
Elevated serum LH	40-51%
Elevated testosterone	29-50%

Table 1: Clinical signs and symptoms of PCOS.

Genetics of PCOS

Ovary and Adrenal Steroidogenesis

CYP11A: Steroidogenesis begins with the conversion of cholesterol to progesterone. P450 is the catalyst. P450 is encoded by the CYP11A gene, which is found at 15q24. Serum testosterone levels are also associated with the CYP11A gene. Additionally, the CYP11A alleles have a correlation with the 5′ untranslated region (5′ UTR) [10].

CYP17A1: The P450c17 enzyme catalyses the conversion of progesterone and pregnenolone via CYP17A1 into

17-hydroxyprogesterone and 17-hydroxypregnenolone, and then back into didehydroepiandrosterone (DHEA) and Δ4-Androstendione (Δ4A). Activities like 17,20-lyase and 17-hydroxylase are exhibited by the P450c17 enzyme. CYP17A encodes P450c17 and is found at 10q27.3. It was announced that ovarian theca cells from women with PCOS have increased P450c17 enzyme expression and activity [10].

CYP19: Androgen is converted into oestrogen by CYP19. Cytochrome P450 aromatase and NADPH cytochrome P450 reductase make up the enzyme complex, and CYP19, which is found at 15p21.1, encodes P450arom. Numerous cases of hyperandrogenism have been linked to aromatase insufficiency. All PCOS follicles have decreased aromatase activation and oestradiol bioactivity when compared to the control follicles [10]. This indicates that excessive androgen causes inappropriate follicle formation and that aromatase activity may be reduced in PCOS follicles.

HSD17B1 & HSD17B2: They are members of the class of enzymes known as alcohol oxidoreductases, which catalyse the steroidogenesis process by dehydrogenating 17-hydroxysteroids. As an example, androstenedione and testosterone, DHEA and androstenediol, and estrone and oestradiol are all interconverted. Without PCOS endometrial therapy, women have been found to express more mRNA producing and inactivating enzyme [11].

HSD3B1 & HSD3B2: The placenta and peripheral tissues express the type I 3β-HSD isoenzyme, while the adrenal gland, ovary, and testis express the type II 3β-HSD isoenzyme. (HSD3B) deficiency is linked to insulin-resistant PCOS in hyperandrogenic females (HF) [11].

StAR: StAR stands for Steroidogenic Acute Regulatory protein. One type of transport protein called StAR moves cholesterol around the mitochondria. Some patients may develop PCOS as a result of a steroidogenesis disorder, which raises the amount of androgen produced by the ovaries and adrenal glands. The StAR is responsible for starting the steroidogenesis process [12].

Steroid Hormone Actions

Androgen receptor: Androgen hypersecretion is one of the most prevalent features of PCOS. The effect of this condition is that the ovary produces too much androgen. It's called hyperandrogenism, and it's the second key factor that causes PCOS. Between 17% and 83% of women suffer from this illness [13].

SHBG: Serum Sex Hormone-Binding Globulin (SHBG) is low in patients with PCOS and hyperandrogenism. Decreases in SHBG levels are a result of hyperinsulinemia linked to PCOS. The liver suppresses the production of SHBG [14].

Gonadotropin Action and Regulation

LH, FSH: One significant feature of PCOS is inappropriate gonadotropin secretion. One of the common causes of PCOS is a high level of LH. Low FSH secretion and excessive LH secretion are characteristics of female PCOS patients. Typically, the ratio utilized to identify aberrant gonadotropin secretion is 2–3/1 [15]. Follicle stimulating hormone (FSH) levels are typically low in PCOS. It is in charge of promoting the development of ovarian follicles. They include developing eggs. A longer duration of FSH deficiency would prevent the follicle from maturing and releasing eggs. Consequently, this would lead to infertility. The ovaries' immature follicles will cause tiny cysts to form [16].

Inhibin βA and Inhibin βB: Insulin resistance is linked to the syndrome known as PCOS. The heterodimer inhibin is in charge of controlling the release of FSH [17]. Inhibin can be released to suppress the rise in FSH concentrations. Inhibin A and Inhibin B are its two variations. It is secreted by the placenta, pituitary gland, gonads, etc. During the follicular phase, Inhibin B is more significant than Inhibin A. Compared to normal women, women with PCOS have higher levels of inhibin [16].

MADH4: Mammal signalling is mediated by the protein known as mothers against decapentaplegic homolog 4. The SAMD family includes the protein. Two functional domains comprise SAMD4. A three-dimensional structure makes up MH1 and MH2 (MAD homology is represented by Regions M and H). This is comparable to the Drosophila protein and SAMD4 in mammals.

Genetic Changes Contributing to the Pathophysiology of PCOS

PCOS is a multifaceted, multifactorial condition determined by both genetic and phenotypic factors. The genetic foundations of polycystic ovary syndrome involve neuroendocrine, metabolic, and reproductive pathways in the disease's progression [18]. Due to recent evolutionary origins, and its trend to run in families, PCOS patients are usually associated with abnormal gene expression. It is important to understand the correlation of genes with PCOS and this can be achieved with the help of next generation sequencing, family focused and genome-wide association studies [19]. The identification of uncommon genetic variations and effective gene networks using next-generation sequencing, alongside studies on epigenetics, has the potential to deepen our comprehension of the genetic basis of PCOS. It is associated with complex pathophysiology influenced by genetic and environmental Genetic Changes Associated with Hyperandrogenism

factors. The genetic changes associated with it interact with association in patients of PCOS, it is important to perform hormonal, metabolic, and ovarian functions, leading to the studies on larger sample size along with genome-wide characteristic symptoms. To further understand the genetic characteristic symptoms. To further understand the genetic association studies (GWAS) [20].

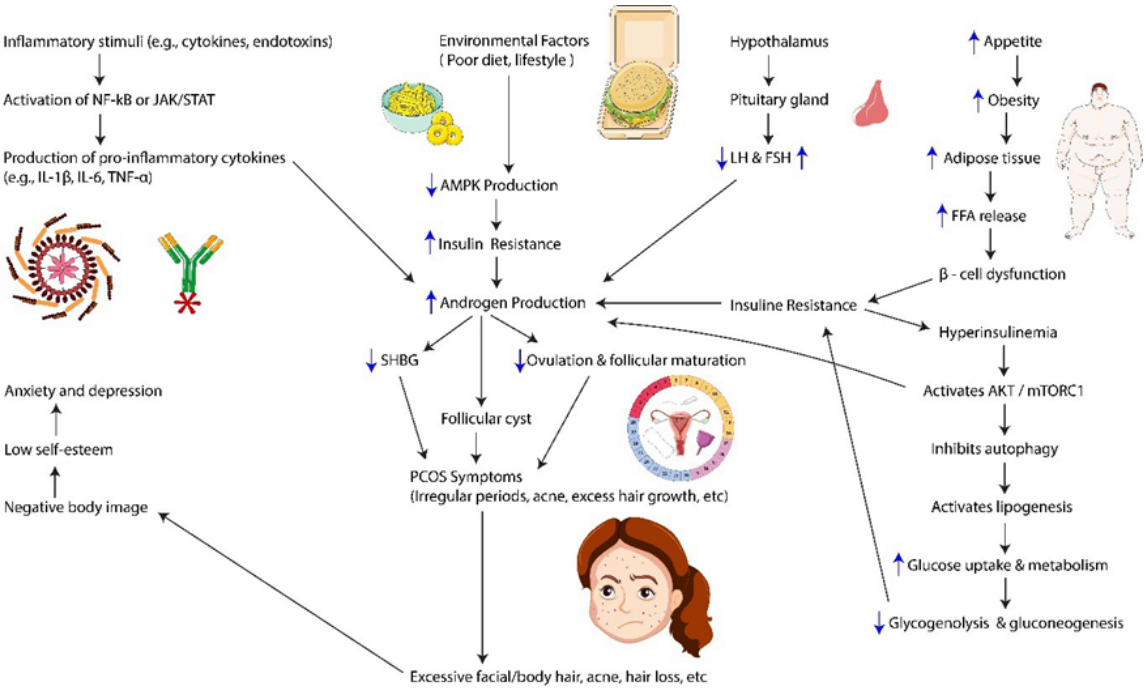

Figure 2: Polycystic Ovary Syndrome: Mechanistic Overview.

Cytochrome P450, family 11, subfamily A, member 1 (CYP11A1): Being present inside the mitochondrial inner membrane, it encodes for cytochrome p450. It helps in conversion of cholesterol to pregnenolone and contributes to steroid synthesis pathway [21].

Variations in this gene increase the production of androgen by ovaries. Ovarian theca cells overproduce testosterone and androstenedione in response to luteinizing hormone (LH) due to genetic alterations in genes regulating steroidogenesis (CYP11A1 and CYP17). This leads to elevated androgen levels, which contributes to symptoms like hirsutism, acne and male pattern baldness [22].

Cytochrome P450, family 17 (CYP17): It is the gene that encodes for P450c17α which is primarily associated with PCOS. This gene converts 17-hydroxyprogesterone to 17 hydroxy pregnenolone which causes hyperandrogenism. Polymorphism of this gene causes increased susceptibility towards PCOS.

Its expression in dysregulated at mRNA stability of theca cells. Also, few studies suggested that there is no correlation between CYP17 gene polymorphism and testosterone levels [23,24].

Androgen receptor gene (AR): Androgen receptor genes are located at the Xq11-q12 region on the X-chromosome [25]. Mutations in this gene can enhance the sensitivity of tissues to androgens, contributing to hyperandrogenism. Increased androgen receptor activity due to genetic variations in the AR gene exacerbates the effects of elevated androgens, worsening hyper androgenic symptoms [26].

Genetic Changes Associated with Ovulatory Dysfunction and Anovulation

Luteinizing hormone receptor gene: Altered LH receptor signalling increases LH levels, disrupting the balance between FSH and LH required for normal ovulation, high levels of these hormones reduce the levels of follicle stimulating hormone. It hinders the reach of androgen to estrogen causing hyperandrogenism in the ovaries [27]. Increased androgen production further inhibits follicular maturation, contributing to the failure of dominant follicle selection and anovulation.

Follicle stimulating hormone receptor (FSHR): FSH receptors are located at chromosome 2 p21-p16 with 10 and 9 exons and introns respectively. Mutation in these receptors destroys the structural protein leading to reduced

FSH production which causes follicular arrest contributing towards progression of PCOS and failure to ovulate [28].

Genetic Changes Associated with Insulin Resistance and Hyperinsulinemia

Insulin receptor gene (INSR): It is a heterotetrametric protein consisting of 2α and 2β subunits in the intrinsic tyrosine kinase domain of insulin receptor. Variants in the insulin receptor gene reduce insulin sensitivity. There is no direct correlation of this gene in PCOS patients but some studies showed its close association with D19S884 which is a microsatellite marker on chromosome 19 p13.2 [29]. Insulin resistance in PCOS is partially due to genetic mutations in genes like INSR and IRS1, leading to decreased responsiveness to insulin in muscle and adipose tissue. As a result, the pancreas compensates by producing more insulin (hyperinsulinemia) [30,31]. Elevated insulin levels stimulate ovarian theca cells to produce more androgens. Insulin also suppresses the production of sex hormone-binding globulin (SHBG) in the liver, increasing free androgens in circulation [32].

Insulin receptor substrate 1 (IRS1): This gene plays a key role in insulin signalling, and mutations can lead to insulin resistance. PCOS patients, defects in pancreatic beta cells contribute to decreased hepatic insulin clearance, thereby leading to insulin resistance. The minisatellite variable number of tandem repeats (VNTR) region on chromosome 11p15.5, located on insulin gene upstream, regulates its expression [33]. Also, some recent studies confirmed a link between this VNTR polymorphism and PCOS in anovulatory women [34].

Peroxisome proliferator- activated receptor gamma (PPAR-γ): It is a nuclear transcription factor pivotal in governing glucose and lipid metabolism. Variants in this gene may lead to increased insulin resistance, altered lipid metabolism and obesity [35].

Genetic Changes Associated with Obesity and Metabolic Syndrome

Melanocortin 4 receptor (MC4R): Variants in this gene are associated with obesity and abnormal energy regulation. Obesity and PCOS are linked to abnormal production of adipokines (e.g., leptin, adiponectin), which contribute to inflammation and metabolic dysfunction [36].

Fat mass and obesity-associated gene (FTO): Fat mass obesity gene as its name indicates, is attributed with obesity and diabetes mellitus type 2. Alpha-ketoglutarate enzyme is encoded by this gene. Obesity and insulin resistance are key characteristics of PCOS and hence FTO is also associated with PCOS [37,38]. Genetic predispositions to obesity (such as mutations in MC4R and FTO) lead to increased adiposity, particularly visceral fat. Obesity further worsens insulin resistance, exacerbating hyperinsulinemia and its downstream effects on androgen production and menstrual irregularities [39].

Genetic Changes Associated with Inflammation

Tumor necrosis factor alpha (TNF-α): Genetic polymorphisms in pro-inflammatory cytokines like TNF-α may contribute to chronic low-grade inflammation in PCOS. PCOS is often associated with elevated levels of inflammatory markers (e.g., C-reactive protein, TNF-α). Genetic predispositions to inflammation, such as variants in cytokine-related genes, contribute to systemic inflammation, which is linked to insulin resistance and cardiovascular risk in women with PCOS [40,41].

Interleukin 6 (IL-6): Variations in this gene are associated with increased inflammatory responses, which can exacerbate metabolic and reproductive symptoms of PCOS. Related clinical manifestations include elevated C- reactive protein, increased risk of cardiovascular disease and inflammatory comorbidities [42].

Genetic Changes Associated with Disrupted Hormonal Feedback Loops

Gonadotropin releasing hormone receptor (GNRHR): Genetic variations in the regulation of GnRH secretion affect the balance between LH and FSH. Genetic changes in the regulation of GnRH lead to increased pulsatile release of LH relative to FSH, disturbing normal folliculogenesis and promoting androgen production by ovarian theca cells [43].

Follicle-Stimulating Hormone Beta-Subunit (FSHB): Mutations in this gene lead to impaired production of FSH. Genetic mutations in GNRHR and FSHB alter the feedback mechanisms of the hypothalamic-pituitary-ovarian axis that regulate the menstrual cycle, contributing to anovulation and menstrual irregularities in PCOS [44].

Sex hormone binding globulin (SHBG): It acts as an initial biomarker in PCOS. It is a 90-100kDA homodimeric glycoprotein produced by liver located at chromosome 17p13-12. Mutation leads to decrease in their levels which in turn increase androgen levels leading to anovulation and other complications in PCOS [45].

Other Genetic Changes Associated with PCOS Like Symptoms

Breast cancer gene 1 and 2 (BRCA): BRCA1 and BRCA2 mutations are not directly involved in the pathophysiology of PCOS, there may be some overlap in how these genetic

mutations affect ovarian function, hormone regulation, and metabolic processes. BRCA mutation carriers face unique reproductive challenges, such as increased risk of ovarian cancer and potential infertility, but their reproductive issues differ from the hormonal and metabolic imbalances driving PCOS. Further research may uncover more nuanced connections between BRCA mutations and PCOS-like features [46].

Cytochrome P450, family 11, subfamily B member 2 (CYP11B2): The CYP11B2 gene encodes the enzyme aldosterone synthase, which is crucial for the biosynthesis of aldosterone, a hormone involved in regulating blood pressure, sodium, and potassium balance. Mutations in CYP11B2 are primarily linked to disorders of aldosterone production, such as familial hyperaldosteronism, and are not directly related to PCOS. However, there are some potential indirect connections between CYP11B2 gene mutations and PCOS, particularly through their influence on hormonal balance and blood pressure regulation [47].

Cytochrome P450, family 21 (CYP21): While PCOS and CYP21 mutations (leading to congenital adrenal hyperplasia) are different conditions, they share key features such as hyperandrogenism, menstrual irregularities, and in some cases, insulin resistance. Both conditions can result in excess androgen production, leading to similar clinical symptoms. However, the source of androgen excess differs: in PCOS, it primarily comes from the ovaries, while in CAH (due to CYP21 mutations), it originates from the adrenal glands. Proper diagnosis and differentiation are essential for appropriate management, as CAH requires specific treatments like glucocorticoids, whereas PCOS management often focuses on lifestyle changes and insulin sensitizers like metformin [48,49].

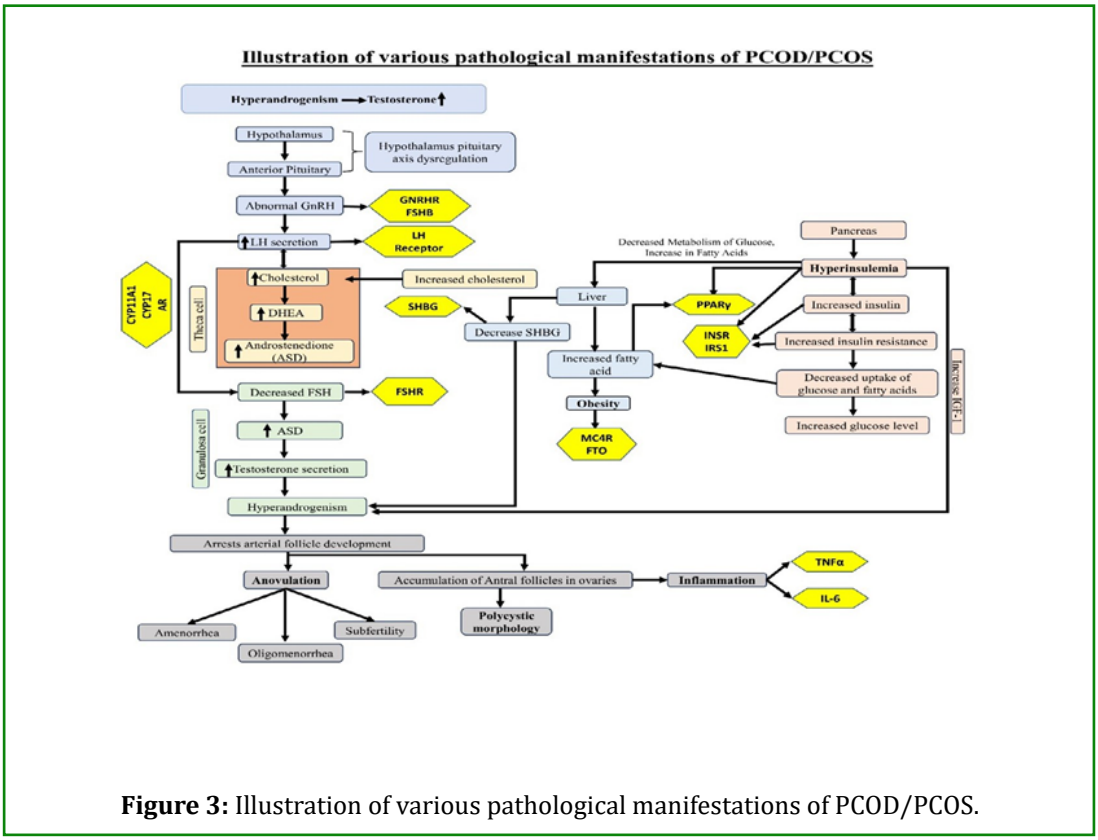

Figure 3: Illustration of various pathological manifestations of PCOD/PCOS.

Diagnosis

Demonstrative measures have been set up by the changed agreement of the National Institutes of Health and Child Health and Human Development (1990) and by agreement models set up during the ESHRE/Rotterdam conference in 2003.

- **NIH 1990:** Chronic anovulation, Clinical and/or biochemical signs of hyperandrogenism (both criteria needed) [50].
- **ROTTERDAM 2003:** Oligo and/or anovulation, Clinical and /or biochemical signs of hyperandrogenism, Polycystic ovaries (two of three criteria needed) [51].
- **AE-PCOS SOCIETY 2006:** Clinical and /or biochemical signs of hyperandrogenism
- Ovarian dysfunction (oligo-anovulation and/or polycystic ovarian morphology) (both criteria needed) The overall pathophysiology of PCOS in relationship to

various genetic changes are illustrated in figure 2.

Phenotypes	1	2	3	4
	Classic	NIH	Ovulatory	Normoandrogenic
Hyperandrogenism	Yes	Yes	Yes	No
Chronic anovulation	Yes	Yes	No	Yes
Polycystic ovaries	Yes	No	Yes	Yes
NIH1990	×	×		
Rotterdam 2003	×	×	×	×
AE-PCO Society 2006	×	×	×	

Table 2: PCOS phenotypes according to each diagnostic criterion.

Current Treatment Options for PCOS take part in daily exercise, addressing behaviour, undergo pharmacological treatment, quitting smoking and alcohol Presently the standard treatment for PCOS includes life style modifications andpharmacological treatments. The existing treatment options for PCOS are modifications and pharmacological treatments. Lifestyle illustrated in table 3. modifications are the first line treatment which include diet, exercise and weight loss. Restriction of calorie consumption,

Therapies	Treatment	References
Insulin Sensitizers	Used to treat hyperinsulinemia Reduces serum androgen and gonadotrophin levels Improves serum lipid and prothrombin factors Improves ovulation, menstrual cycle and fertility Commonly used Insulin sensitizers: Metformin, myo-inositol, thiazolidinediones	[52,53]
Oral contraceptives	Combined oral contraceptive pills supress androgen production Treats endocrine abnormalities and other symptoms like hirsutism and acne Includes combination of progesterone and estrogen pills Has some side effects like decreased insulin sensitivity	[54]
Antiandrogens	Used to manage PCOS symptoms and related conditions such as acne, hirsutism, and alopecia. Has anti-inflammatory actions Drugs usually used are cyproterone acetate, spironolactone, finasteride, and flutamide Have both positive as well as negative effects	[55]
Assisted Reproductive Technology	- Third-line of treatment for PCOS Gonadotrophin hormones are used to stimulate production of multiple follicles Also includes In-vitro fertilization with or without intracytoplasmic sperm injection	[56]
Dietary Therapy	Healthy diet, along with exercise and life style modification reduce symptoms of PCOS Bariatric surgeries offer additional help to obese patients	[57]

Table 3: Treatment options for the improvement of PCOS.

Future Directions

PCOS is a lifelong condition with no cure and ongoing complications. There is an urgent need in improvement of these available diagnostic and therapeutic options for the upcoming generation. Improved personalized therapies can advance quality of life and better diagnostic techniques can help in early detection further reducing the risk of

comorbidities. Use of GWAS, Next-generation sequencing can help in identifying the disrupted genes and pathways. Gut microbiota significantly contributes to the progression of PCOS, therefore, research on personalized therapies with pre and probiotics to maintain gut microbiota as well as symptoms of PCOS. Therapies including statins, inositol, IL22 and miRNA are under clinical trial which in future can potentially help in management of polycystic conditions [58,59]. Long term health monitoring for associated risks such as cardiovascular diseases and diabetes can help to improve overall outcomes in PCOS patients.

Conclusion

The pathophysiology of PCOS involves a complex interplay of genetic changes that affect multiple physiological pathways. These genetic factors lead to hormonal imbalances (hyperandrogenism, LH/FSH ratio disruption), metabolic disturbances (insulin resistance, obesity), and ovarian dysfunction (anovulation, polycystic ovaries), all of which contribute to the clinical manifestations of PCOS, such as menstrual irregularities, infertility, hirsutism, and metabolic syndrome.

In conclusion, PCOS being an incurable disorder, it is crucial to identify and comprehend the genetic factors contributing to the development of PCOS. This can potentially lead to develop targeted therapies and personalized treatments to improve the patient outcomes. Additional research in this field holds the potential to reveal new understanding of the disease's progression, leading to more effective interventions. Moreover, understanding the genetic aspects can help in early diagnosis, prevention and reduce long term health risks associated with PCOS. By expanding research, it will be easy to incorporate the genetic findings with the clinical practices to provide better interventions to the affected women.

Conflict of Interest

There are no conflicts of interest

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