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Review Article

Polycystic Ovarian Disease: A Comprehensive Review of Pathophysiology, Diagnosis, and Management

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ABSTRACT

Polycystic ovarian syndrome (PCOS) is an endocrine disorder that impacts women during their reproductive years. Diagnosing PCOS early can be challenging due to its overlapping symptoms. The Rotterdam Consensus is the most widely accepted diagnostic guideline, which states that a positive diagnosis of PCOS can be made if a patient exhibits two of the following three symptoms: clinical and biochemical signs of hyperandrogenism, oligomenorrhea or anovulation, and polycystic ovarian morphology on ultrasound. Factors such as genetic variations, epigenetic modifications, and lifestyle disruptions contribute to pathophysiological issues in women with PCOS, including hyperandrogenism, insulin resistance, and chronic inflammation. At the molecular level, various proteins and signaling pathways are implicated in the progression of the disease, complicating the efficacy of a singular genetic diagnostic method. Recent advancements in the genetic understanding of PCOS have identified four phenotypic forms, categorizing patients into classic, ovulatory, and non-hyperandrogenic types. Genetic investigations pinpoint the underlying causes of PCOS, which has been shown to have an autosomal dominant pattern, although recent studies suggest it arises from multiple genes. Genome-wide association studies (GWAS) have reshaped the understanding of diagnosis and treatment for this reproductive and metabolic disorder. This review examines several genes linked either directly or indirectly to the development and progression of PCOS.

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine condition that impacts women in their reproductive years. This syndrome manifests through various symptoms, such as irregular menstrual cycles, elevated levels of male hormones, and the appearance of polycystic ovaries seen on ultrasound. Diagnosis typically follows the Rotterdam criteria, which stipulate that

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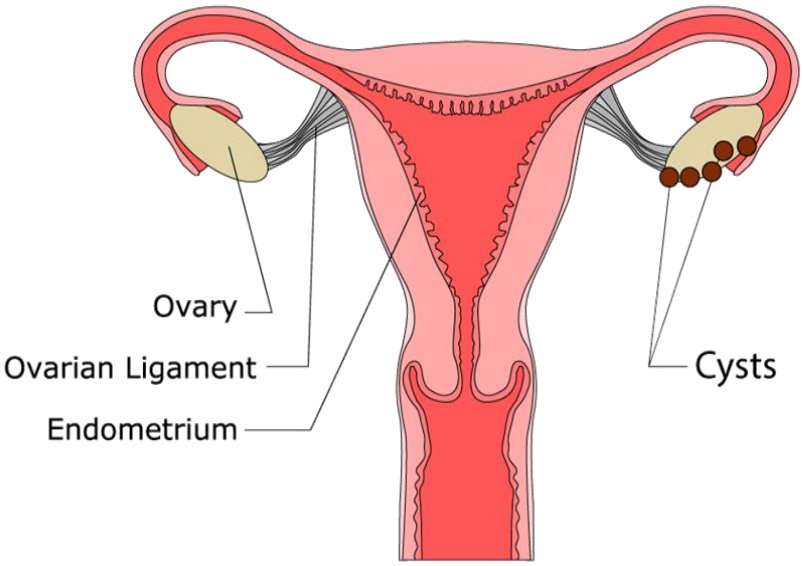
at least two of the following three characteristics must be present: infrequent or absent ovulation, signs of high androgen levels (either clinical or biochemical), and the detection of polycystic ovaries (indicated by having 12 or more follicles in each ovary or an ovarian volume exceeding 10 cm^3). Additionally, PCOS is linked to metabolic issues, including insulin resistance, obesity, and an elevated risk of developing type 2 diabetes and cardiovascular diseases. Although the modern history of polycystic ovary syndrome (PCOS) started with the pivotal paper by Stein and Leventhal in 1935,[1] there are suggestions that the "syndrome" was referred to as early as in the time of Hippocrates (ca. 460–377 BC). Medical notes at the time referred to women "whose menstruation is less than three days or is meager, are robust, with a healthy complexion and a masculine appearance; yet they are not concerned about bearing children nor do they become pregnant" and suggest that they may have been describing women with PCOS.[2].PCOS seems to have dated back to the 1700's , however, formal diagnosis criteria was not presented until the 1990's.1721 An Italian physician and medical scientist named Vallisneri described, "a married, infertile woman with shiny ovaries with a white surface and the size of ovaries as pigeon eggs" .1844 Bulius and Kretschmar described the presence of nests or clusters in the ovaries, also known as hyperthecosis.1879 Lawson Tait suggested total removal of the ovaries to treat these cysts.1915 Total ovarian resection is criticized, John McGlinn suggests puncturing the cysts on the surface.1935- Stein and Leventhal. Presented a group of seven women with similar characteristics such as hirsutism, menstrual disturbances, and enlarged ovaries with the presence of follicles. Suggested using an ovarian wedge resection for treatment. Method showed to be successful in regulating menstrual cycles.1990's National Institutes of Health (NIH) held PCOS conference to create and propose formal diagnosis criteria. NIH criteria includes: symptoms of excess androgens, rare ovulations, and exclusion of other disorders with similar clinical symptoms.2003 Rotterdam criteria is created during a PCOS conference in the Netherlands. Criteria is broader and more inclusive. This criteria is still the most widely used and accepted. Global Prevalence of PCOD/PCOS in Different Populations. Population Group Prevalence Rate (%) Notes. General Global Estimate 4% – 20% Varies based on diagnostic criteria (NIH, Rotterdam, AES). India 3.7% – 22.5% Higher prevalence in urban areas, lifestyle changes a major factor. United States 6% – 15% Based on NIH or Rotterdam criteria; higher prevalence in overweight/obese women. China 5% – 10% Urban-rural variation seen. Middle East (e.g., Iran, UAE) 7% – 25% Higher rates possibly due to genetic and lifestyle factors. Australia 8% – 13% Higher prevalence noted among adolescents and obese women. Europe (UK, Spain, Italy) 6% – 15% Prevalence influenced by lifestyle and ethnicity. African Populations 3% – 10% Limited studies, but rising rates with urbanization. Latina/Hispanic Women (USA) Up to 15% Higher rates of metabolic complications also observed.

2. Etiology

The origins of Polycystic Ovarian Disease (PCOD), commonly known as Polycystic Ovary Syndrome (PCOS), are intricate and involve multiple elements, including genetics, hormones, metabolism, and environmental factors. Although the precise cause is not fully understood, studies indicate that PCOD arises from various interacting influences that interfere with typical ovarian and endocrine operations.

2.1 Insulin resistance and it's role

Insulin resistance (IR) is a central pathophysiological feature in the development of Polycystic Ovarian Disease (PCOD), affecting both reproductive and metabolic aspects of the disorder. Insulin resistance refers to a state where the body's tissues, particularly muscle, adipose, and liver cells, exhibit a diminished response to the action of insulin. As a compensatory mechanism, the pancreas secretes higher amounts of insulin, leading to a state of hyperinsulinemia. This hyperinsulinemia plays a critical role in the development and progression of PCOD by directly influencing ovarian function, specifically by stimulating theca cells in the ovaries to increase androgen production. Elevated androgen levels disrupt normal follicular development, resulting in anovulation, menstrual irregularities, and the characteristic polycystic appearance of the ovaries. Moreover, insulin has been shown to reduce hepatic production of sex hormone-binding globulin (SHBG), which increases the concentration of free, biologically active androgens in circulation. This further contributes to clinical manifestations of PCOD such as hirsutism, acne, and alopecia . Importantly, insulin resistance is observed not only in obese women with PCOD but also in lean individuals, suggesting an intrinsic metabolic defect in insulin action in these women . Genetic factors also play a significant role, with polymorphisms in the insulin receptor (INSR) gene and other genes regulating insulin signaling pathways contributing to the development of insulin resistance in PCOD.



Beyond reproductive consequences, insulin resistance in PCOD significantly increases the risk of metabolic disorders such as impaired glucose tolerance, type 2 diabetes mellitus, dyslipidemia, and cardiovascular disease. Chronic hyperinsulinemia contributes to a pro-inflammatory state and promotes visceral adiposity, both of which exacerbate insulin resistance and metabolic dysfunction. Addressing insulin resistance through lifestyle interventions, such as weight loss, dietary modifications, and exercise, is a cornerstone of PCOD management. Additionally, pharmacological agents like metformin are widely used to improve insulin sensitivity, reduce androgen levels, and restore ovulatory function in affected women.

2.2 Hormonal imbalance

Hormonal imbalance is a key characteristic of Polycystic Ovarian Disease (PCOD) and significantly influences its causes and symptoms. A notable hormonal issue in PCOD is hyperandrogenism, which involves heightened levels of male hormones, especially testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS). These androgens are mainly generated by the ovarian theca cells, stimulated by luteinizing hormone (LH). In PCOD, the ovaries respond excessively to LH, leading to increased androgen production, which results in symptoms such as excessive hair growth (hirsutism), acne, hair loss (alopecia), and irregular ovulation. Another significant hormonal change associated with PCOD is the altered secretion of gonadotropins, characterized by an increase in both the frequency and intensity of pulsatile release of gonadotropin-releasing hormone (GnRH). This alteration results in a heightened ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH), often surpassing 2:1 or 3:1 in women affected by the condition. The relative shortage of FSH hinders adequate follicular development, which leads to arrested follicular growth, anovulation, and the development of multiple small cystic follicles within the ovaries. Insulin resistance and elevated insulin levels, frequently observed in PCOD, worsen hormonal dysregulation by enhancing the production of androgens in the ovaries and diminishing the liver's production of sex hormone-binding globulin (SHBG). A decrease in SHBG leads to higher availability of circulating androgens, which amplifies the symptoms associated with hyperandrogenism. Additionally, increased insulin levels work together with LH to further boost androgen synthesis in the theca cells. This interplay contributes to the complex hormonal challenges faced by individuals with PCOD.

2.3 Environmental influences

Environmental elements are increasingly recognized as possible factors in the onset and advancement of Polycystic Ovarian Disease (PCOD), interacting with genetic, metabolic, and hormonal processes. Key environmental factors studied include endocrine-disrupting chemicals (EDCs), eating habits, lack of physical activity, and psychosocial stress. Each of these may play a role in the development of PCOD. Endocrine-disrupting chemicals (EDCs), including substances like bisphenol A (BPA), phthalates, polychlorinated biphenyls (PCBs), and pesticides, are pollutants in the environment that can disturb the normal operation of the endocrine system. BPA, often present in plastic materials and food wrapping, is known to imitate estrogen and influence androgen and insulin signaling pathways, which may hinder ovarian follicle development and steroid production. Numerous studies indicate that women with polycystic ovary disease (PCOD) have elevated serum BPA levels compared to healthy individuals, implying a connection between EDC exposure and the hormonal as well as metabolic irregularities observed in PCOD. Besides chemical exposure, a person’s diet and nutritional health play a crucial role in the risk of developing PCOD. A diet high in processed foods, trans fats, and refined sugars, combined with a low intake of fiber, fruits, and vegetables, is linked to greater insulin resistance, weight gain, and heightened inflammation, which can worsen PCOD symptoms. On the other hand, consuming a diet abundant in whole grains, lean protein, and omega-3 fatty acids has been associated with better metabolic and reproductive results for those with PCOD. Excess body weight, especially central or visceral fat, is a significant environmental contributor to PCOD. Although PCOD can also affect women with a normal weight, increased body fat intensifies insulin

resistance and excess androgen levels, resulting in more pronounced symptoms. Additionally, a lack of physical activity promotes weight gain and metabolic issues, underscoring the crucial role of exercise in both preventing and managing PCOD.

Different Genes Involved in Pathogenesis of PCOS.

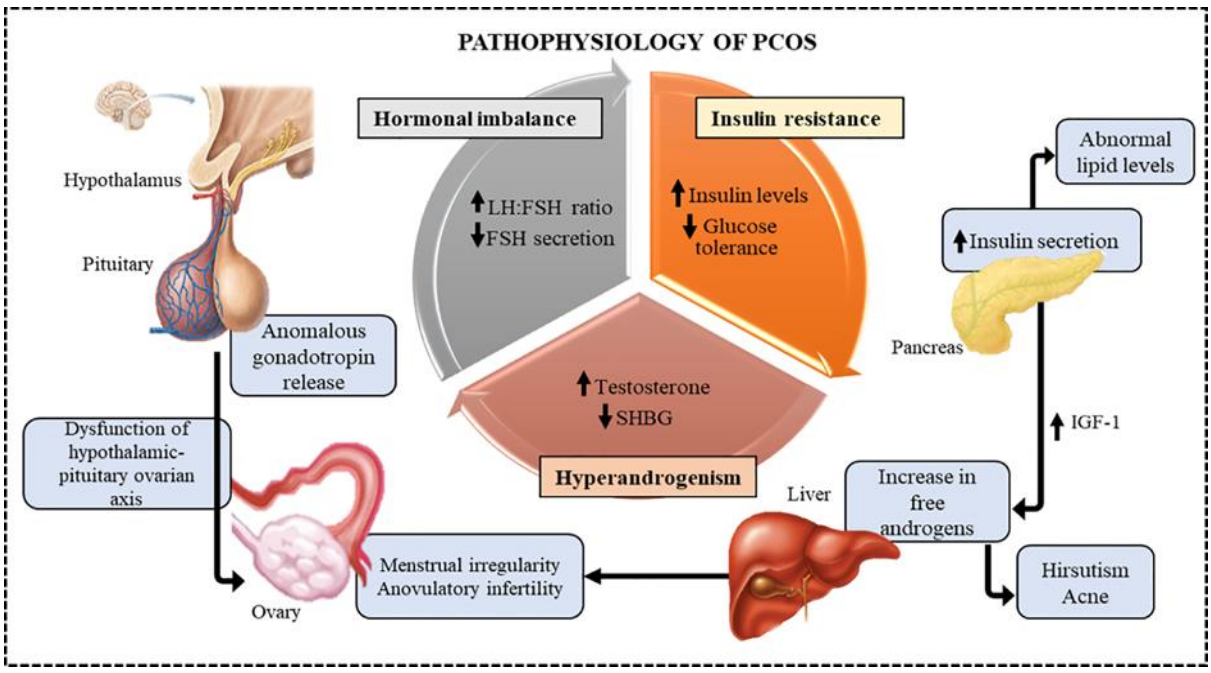
S.N	Different Gene Categories Involved in PCOS	Genes under Categories
1.	Genes involved in ovarian and adrenal steroidogenesis	i. CYP19 ii. CYP17 iii. CYP21 iv. CYP11a
2.	Epigenetics of PCOS	i. NCOR1 ii. PPARG1
3.	Gene involved in insulin action and secretion	i. CAPN10 ii. IRS-1 iii. IRS-2 iv. INS v. INS
4.	Gene involved in steroid hormone effect	i. AR ii. SHBG
5.	Gene involved in gonadotropin	1. LH 2. AMH 3. FSHR
6.	Other genes	1. FTO 2. PCO 3. SRD5A 4. SRD5B

3. Pathophysiology

The pathophysiology of Polycystic Ovarian Disease (PCOD), commonly known as Polycystic Ovary Syndrome (PCOS), is intricate and involves multiple factors, including genetic predispositions, hormonal imbalances, metabolic issues, and environmental influences that play a role in its onset and progression. Central to PCOD is an imbalance within the hypothalamic-pituitary-ovarian (HPO) axis, resulting in more frequent and pronounced pulses of gonadotropin-releasing hormone (GnRH). Consequently, this leads to a greater release of luteinizing hormone (LH) compared to follicle-stimulating hormone (FSH) from the pituitary gland. The heightened levels of LH prompt the ovarian theca cells to generate excessive amounts of androgens, such as testosterone and androstenedione, contributing to the hyperandrogenism typically associated with PCOD.

2.1 Ovarian Dysfunction

Ovarian dysfunction is a key feature of Polycystic Ovarian Disease (PCOD) and significantly impacts the reproductive and hormonal irregularities seen in women with this condition. In the context of PCOD, ovarian dysfunction mainly encompasses ongoing anovulation, irregular menstrual patterns, and hindered follicular maturation. These issues are critical factors that lead to challenges in conception and reduced fertility. The development of ovarian dysfunction in polycystic ovary syndrome (PCOS) is intricately associated with the irregular functioning of the hypothalamic-pituitary-ovarian (HPO) axis. In individuals with PCOS, there is an increased release of gonadotropin-releasing hormone (GnRH) in a pulsatile manner, which disrupts the balance of gonadotropins, causing luteinizing hormone (LH) levels to rise disproportionately compared to follicle-stimulating hormone (FSH). The heightened LH levels lead to overstimulation of the ovarian theca cells, causing an overproduction of androgens. Concurrently, the relative lack of FSH hinders the proper growth and maturation of ovarian follicles. Inadequate support from FSH leads to the halting of developing follicles in the preantral or small antral phase, preventing their advancement to ovulation. This stagnation causes the presence of numerous small, immature follicles on the ovaries, which creates the typical "polycystic" look seen in ultrasound examinations. It is important to note that these cysts are not genuine cysts but rather dormant follicles that are encased in a thickened ovarian stroma. Hyperandrogenism also plays a direct role in ovarian dysfunction by disrupting the typical functions of granulosa cells, diminishing aromatase activity, and negatively affecting follicular development and oocyte quality. Increased levels of androgens within the ovaries further lead to follicular stagnation and hinder the identification of a dominant follicle, ultimately sustaining anovulation. An additional factor related to ovarian dysfunction is the increased presence of Anti-Müllerian Hormone (AMH) frequently noted in women with Polycystic Ovarian Disease (PCOD). AMH is produced by the granulosa cells in pre-antral and small antral follicles, acting as an indicator of the ovarian reserve. In cases of PCOD, elevated AMH levels indicate a surplus of small follicles, which may decrease sensitivity to Follicle-Stimulating Hormone (FSH), consequently hindering both follicular maturation and ovulation processes.



Schematic depiction of PCOS linked mechanism. (Walters et al., 2018, Barber et al., 2016, Rojas et al., 2014).

2.2 Hyperandrogenism

Hyperandrogenism refers to an abnormal increase in male sex hormones (androgens) in females and is a key characteristic of Polycystic Ovarian Disease (PCOD), significantly influencing its clinical features and underlying mechanisms. The main androgens associated with this condition are testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS). In women diagnosed with PCOD, the hyperandrogenism primarily originates from the ovaries, although contributions from the adrenal glands may be observed in certain instances. This hormonal imbalance is crucial for understanding the complexities of PCOD and its symptoms. The mechanism behind hyperandrogenism in PCOD is related to the dysfunction of the hypothalamic-pituitary-ovarian axis. This dysfunction causes an increase in the pulsatile release of gonadotropin-releasing hormone (GnRH), resulting in higher luteinizing hormone (LH) levels compared to follicle-stimulating hormone (FSH). Elevated LH stimulates ovarian theca cells to produce excess androgens. Additionally, insulin resistance, often seen in PCOD, leads to increased insulin levels, which further drives androgen production and reduces the liver's production of sex hormone-binding globulin (SHBG). The lower SHBG levels lead to a rise in free androgens in the bloodstream, intensifying hyperandrogenic symptoms. Hyperandrogenism clinically presents with symptoms such as hirsutism (male-pattern hair growth), acne, androgenic alopecia (thinning of hair on the scalp), and, in more serious instances, virilization. These symptoms can profoundly affect the quality of life and mental health of women who are affected. Laboratory tests often reveal increased levels of serum total testosterone, free testosterone, and DHEAS. However, it's important to note that not all women displaying clinical signs will have biochemical confirmation of hyperandrogenism in their test results. Strategies for managing hyperandrogenism consist of using combined oral contraceptives to reduce ovarian androgen synthesis, anti-androgen drugs like spironolactone, and insulin-sensitizing medications such as metformin to tackle related

insulin resistance. Timely identification and treatment of hyperandrogenism are crucial to lessen the potential long-term effects on reproductive health, metabolism, and mental well-being linked to PCOD.

2.3 Role of Adipose tissue

Adipose tissue is integral to the complex mechanisms behind Polycystic Ovarian Disease (PCOD), serving not just as a reservoir for energy but also functioning as an active endocrine organ that impacts both metabolic and reproductive health. Women suffering from PCOD often present with an accumulation of excess fat, especially in the visceral or central regions, which is linked to the worsening of the syndrome's hormonal and metabolic irregularities. This multifaceted role highlights how adipose tissue contributes significantly to the disease's overall pathology, making it a critical factor to consider in both diagnosis and treatment strategies. Adipose tissue plays a significant role in the development of insulin resistance in PCOD. Adipocytes, particularly those found in visceral fat, produce various bioactive compounds called adipokines, which include leptin, adiponectin, resistin, and inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). In the context of PCOD, an imbalance in these adipokines, along with a rise in free fatty acid release from adipose tissue, leads to systemic insulin resistance and persistent low-grade inflammation. The hyperinsulinemia that occurs stimulates the ovarian theca cells, leading to an overproduction of androgens and exacerbating hyperandrogenism, a key characteristic of PCOD. Additionally, insulin resistance diminishes the liver's ability to produce sex hormone-binding globulin (SHBG), resulting in elevated levels of free androgens in circulation, which intensifies the hormonal imbalance. Beyond its metabolic functions, adipose tissue acts as a peripheral location for the conversion of androgens into estrogens, facilitated by the enzyme aromatase. In females with PCOD, however, elevated levels of androgens surpass the capacity of the aromatase pathway, resulting in a hormonal environment that is skewed towards androgens. Additionally, the buildup of visceral fat further intensifies issues such as irregular menstrual cycles, anovulation, and infertility. Obesity plays a crucial role in worsening PCOD symptoms, but it is not a necessary condition for the disorder itself. When obesity is present, it can intensify insulin resistance, increase androgen levels, and disrupt reproductive functions, often resulting in a more pronounced form of PCOD. Research indicates that issues with adipose tissue in PCOD might initiate at a young age, potentially starting during fetal development. Prenatal exposure to elevated androgen levels could predispose individuals to later issues with body fat accumulation and metabolic irregularities.

3.4 Impact of Inflammation and Oxidation Stress

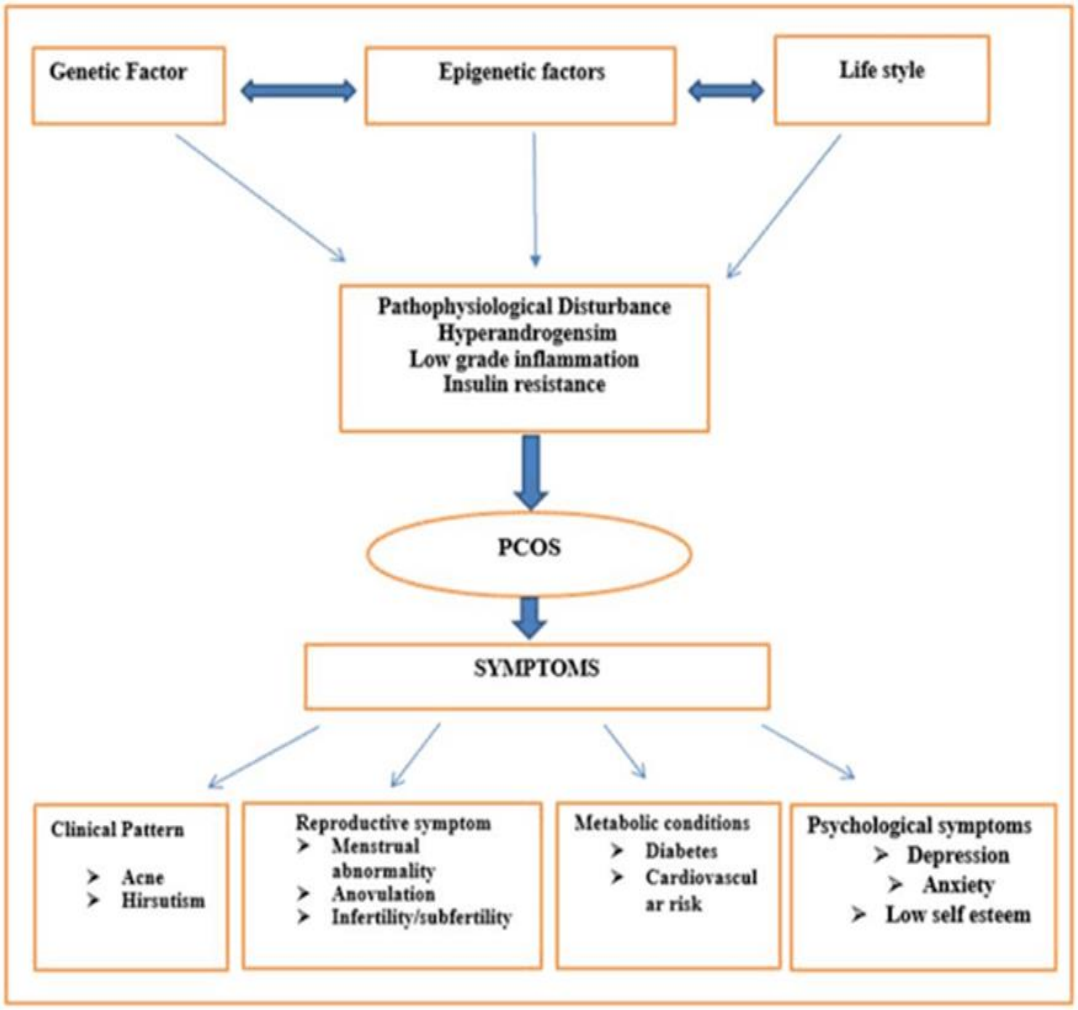
Chronic low-level inflammation and oxidative stress have been identified as significant factors in the development of Polycystic Ovarian Disease (PCOD). These issues contribute substantially to the metabolic, hormonal, and reproductive challenges observed in women with the condition. Research has demonstrated that women suffering from PCOD have increased levels of systemic inflammation markers, regardless of their weight, indicating that inflammation is a fundamental aspect of the disease itself rather than merely a result of excess body fat. Dysfunction of adipose tissue, especially in women with central obesity a frequent characteristic of PCOD results in the heightened release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α),

interleukin-6 (IL-6), and C reactive protein (CRP). These substances foster a persistent state of low-grade systemic inflammation, which impairs insulin signaling pathways at the cellular level, leading to insulin resistance. This condition of elevated insulin levels further stimulates the production of ovarian androgens, thereby maintaining hyperandrogenism and causing reproductive challenges. Beyond inflammation, oxidative stress is increasingly recognized as a significant factor in the development of PCOD (Polycystic Ovarian Disease). This condition arises from an imbalance in the generation of reactive oxygen species (ROS) and the body's ability to combat oxidative damage with antioxidants. Studies have consistently shown that women affected by PCOD exhibit elevated levels of oxidative stress markers, such as malondialdehyde (MDA), alongside depleted antioxidant levels like superoxide dismutase (SOD) and glutathione. The resulting oxidative state plays a pivotal role not only in promoting insulin resistance but also in disrupting the development of ovarian follicles and the quality of oocytes, thereby negatively affecting fertility. Oxidative stress contributes to endothelial dysfunction, heightening the likelihood of cardiovascular issues a well-established long term effect of PCOD. Additionally, research indicates that oxidative stress may facilitate the formation of advanced glycation end-products (AGEs), which can disrupt ovarian function and worsen hormonal imbalances. The interplay between chronic inflammation and oxidative stress creates a detrimental cycle that intensifies insulin resistance, hyperandrogenism, irregular menstrual cycles, and infertility. This cycle also raises the risk of enduring metabolic problems, such as type 2 diabetes and heart disease.

4. Clinical Symptoms

Polycystic Ovarian Disease (PCOD), commonly known as Polycystic Ovary Syndrome (PCOS), exhibits a diverse array of symptoms that can differ significantly in severity and combination among those affected. These symptoms arise from the intricate interactions of hormonal, metabolic, and ovarian issues inherent to the condition. Notable clinical signs typically include irregularities in menstrual cycles, elevated androgen levels, challenges with fertility, weight gain, and various metabolic anomalies. A key characteristic of PCOD is the irregularity of menstrual cycles, often seen as oligomenorrhea (less frequent cycles) or amenorrhea (no menstruation). This occurs mainly due to chronic anovulation, which refers to the ovaries' inability to release eggs consistently, leading to cycle disruption. In addition, some women may encounter extended periods of bleeding or dysfunctional uterine bleeding. Hyperandrogenism, which can be observed both through clinical signs and biochemical tests, is a significant indicator of certain conditions. Clinically, it manifests as hirsutism (abnormal hair growth in areas typical for males, including the face, chest, and back), acne, and androgenic alopecia (reduction in hair volume on the scalp). From a biochemical perspective, laboratory assessments frequently reveal increased concentrations of circulating androgens, particularly testosterone. Infertility is a prevalent issue for women with PCOD, mainly due to persistent anovulation. In cases where ovulation occurs sporadically, the quality of eggs and the uterine conditions may be less than optimal, which decreases the chances of becoming pregnant. Obesity, especially central or abdominal obesity, is often seen in individuals with PCOD, though it is not always the case. Research indicates that around 40–70% of women affected by PCOD are either overweight or obese, typically favouring visceral fat buildup. This excess weight not only

intensifies the reproductive symptoms of PCOD but also greatly aggravates the related metabolic issues. Metabolic disorders are becoming more prominent in understanding the clinical aspects of PCOD. Key issues include insulin resistance, issues with glucose tolerance, the onset of type 2 diabetes, and dyslipidemia, which is marked by high triglyceride levels, reduced high-density lipoprotein (HDL) cholesterol, and elevated low-density lipoprotein (LDL) cholesterol.

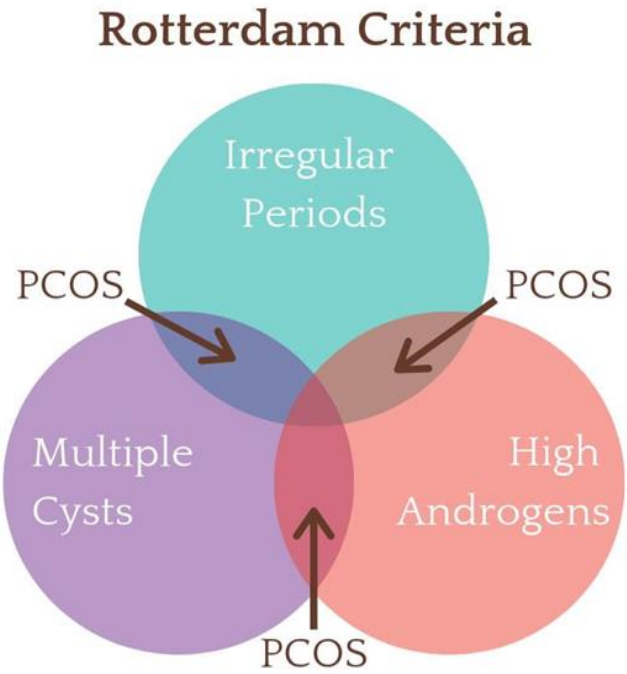


(a)

The presence of these metabolic risk factors significantly increases the long-term risk of cardiovascular disease in women with PCOD. Ultrasound findings of polycystic ovarian morphology reveal enlarged ovaries with numerous small follicles (ranging from 2 to 9 mm) located around the edges, frequently likened to a "string of pearls." However, identifying polycystic ovaries through ultrasound alone does not confirm a diagnosis of PCOD; it must be evaluated in conjunction with both clinical assessments and biochemical data. Additionally, psychological issues such as depression, anxiety, low self-worth, and disturbances in body image are common among women with PCOD, often stemming from the emotional stress related to physical complications like hirsutism, weight gain, and infertility issues.

5. Diagnosis

The identification of Polycystic Ovarian Disease (PCOD), often known as Polycystic Ovary Syndrome (PCOS), relies mainly on a combination of clinical signs, biochemical analyses, and imaging techniques. Various diagnostic standards have emerged over time, with the Rotterdam criteria, introduced in 2003 by the European Society of Human Reproduction and Embryology (ESHRE) alongside the American Society for Reproductive Medicine (ASRM), being the most widely recognized. The identification of Polycystic Ovarian Disease (PCOD), also known as Polycystic Ovary Syndrome (PCOS), relies mainly on clinical signs, laboratory tests, and imaging techniques. Various diagnostic standards have emerged over time, but the Rotterdam criteria, which were set forth in 2003 by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), remain the most widely recognized. Per the Rotterdam criteria, diagnosing PCOD necessitates the identification of at least two out of three specified characteristics: (1) oligo- or anovulation, (2) symptoms of hyperandrogenism, whether clinical or biochemical, and (3) the presence of polycystic ovarian morphology (PCOM) visible in ultrasound examinations, following the elimination of alternative causes of hyperandrogenism like congenital adrenal hyperplasia, androgen-producing tumors, or Cushing's syndrome. Irregular menstrual patterns, particularly oligomenorrhea (fewer than nine periods annually) or amenorrhea (not menstruating for three months or longer), frequently serve as initial clinical signs of PCOD, indicating ongoing anovulation.



Hyperandrogenism can be identified through various clinical manifestations, including excess hair growth (hirsutism), skin issues like acne, and male-pattern hair loss (androgenic alopecia), alongside biochemical assessments. Lab results often show increased levels of total or free testosterone, dehydroepiandrosterone sulfate (DHEAS), or androstenedione. It's important to note that the intensity of hyperandrogenism can differ among individuals, and biochemical results should be interpreted carefully, taking into account factors such as age and body mass index. The

observation of polycystic ovarian morphology through transvaginal or pelvic ultrasound is a key aspect of diagnosis. For polycystic ovarian morphology (PCOM) to be confirmed, there should be at least 20 follicles ranging from 2 to 9 mm in size, and/or one ovary must have a volume exceeding 10 mL. However, it is essential to understand that the mere identification of polycystic ovaries via ultrasound is inadequate for a diagnosis on its own; it should be evaluated in conjunction with clinical signs and biochemical assessments. Besides the primary criteria, evaluating metabolic factors is crucial since numerous women with PCOD experience insulin resistance, compromised glucose tolerance, lipid abnormalities, and a heightened risk for type 2 diabetes. It is advisable to conduct tests such as oral glucose tolerance testing (OGTT), fasting insulin levels, lipid profiles, and measurements of body mass index (BMI), particularly for those who are overweight or obese. Alternative diagnostic methods may involve assessing serum levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). A heightened LH to FSH ratio (greater than 2:1) is commonly associated with PCOD, although this indicator may not always be dependable for conclusive diagnosis. It is vital to rule out other endocrine conditions that can present similar symptoms to PCOD. These include thyroid disorders, hyperprolactinemia, and late-onset congenital adrenal hyperplasia, all of which should be evaluated through proper biochemical assessments. To diagnose PCOD, a thorough assessment is needed, which includes reviewing medical history, conducting physical exams, performing lab tests, and utilizing imaging techniques. The Rotterdam criteria offer a versatile and well-accepted approach, facilitating the identification of the diverse manifestations of the condition.

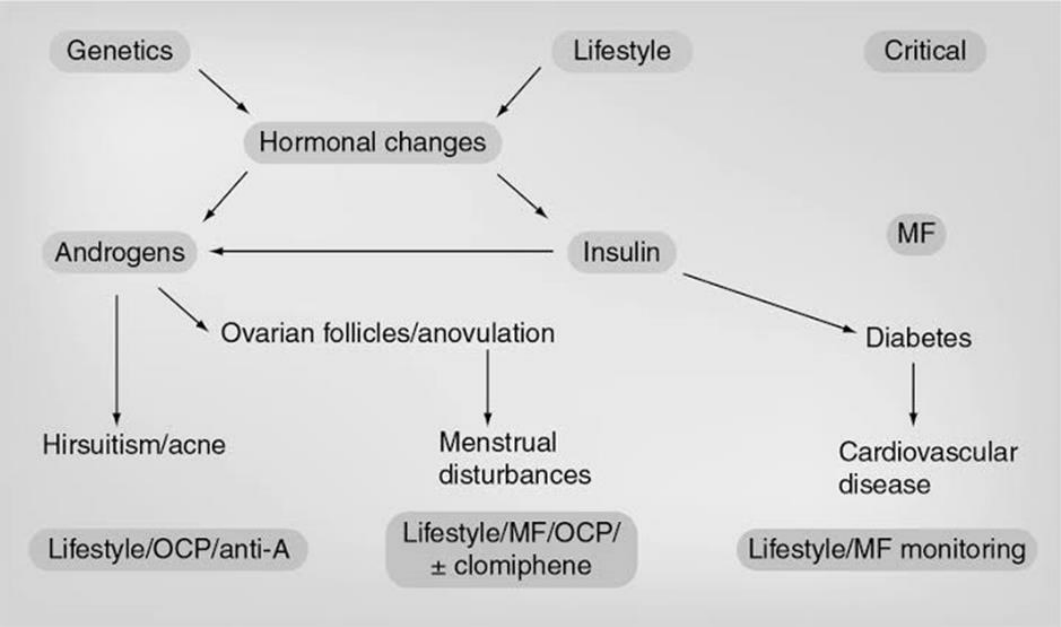
6. Management and Treatment

The management of Polycystic Ovarian Disease (PCOD), often referred to as Polycystic Ovary Syndrome (PCOS), involves a comprehensive approach focused on the individual's unique symptoms, enhancing reproductive results, controlling metabolic issues, and minimizing future health threats. Due to the varied nature of PCOD, a tailored strategy that targets specific symptoms is advisable. The primary approach for treating women with PCOD, particularly those who are overweight or obese, is to implement lifestyle changes, which encompass dietary adjustments, physical activity, and behavioral strategies. Even a modest weight reduction of 5–10% from one's starting weight has been proven to significantly enhance menstrual regularity, ovulation, insulin sensitivity, and symptoms related to hyperandrogenism. Engaging in regular exercise and making dietary modifications that emphasize lower caloric intake, foods with a low glycemic index, and a balanced ratio of macronutrients are essential for managing symptoms and lowering metabolic risks.

6.1 Lifestyle Modification

Lifestyle changes are considered fundamental in managing Polycystic Ovarian Disease (PCOD), or Polycystic Ovary Syndrome (PCOS), particularly for those who are overweight or obese. Given that key characteristics of PCOD include insulin resistance, high androgen levels, and metabolic issues, adopting non-drug approaches like dietary adjustments, physical activity, and behavioral modifications is essential to enhance both reproductive health and metabolic function. Dietary changes play a crucial role in managing lifestyle conditions. Research indicates that a modest weight loss of 5-10% of one’s initial body weight can lead to notable enhancements in menstrual cycles, ovulation, insulin sensitivity, and lower androgen levels. Various dietary

strategies have been investigated for managing PCOD, highlighting the importance of calorie restriction and low glycemic index (GI) diets. These low GI diets can enhance insulin sensitivity and potentially lower circulating androgen levels, which may help restore ovulatory function. Furthermore, the Mediterranean diet which emphasizes an abundance of fruits, vegetables, whole grains, lean proteins, and healthy fats has been linked to improved metabolic outcomes and decreased inflammation among women dealing with PCOD.



Engaging in regular physical activity is a crucial aspect of changing one's lifestyle. Research indicates that consistent aerobic workouts and strength training boost insulin sensitivity, decrease abdominal fat, and help regulate menstrual cycles. When combined, dietary modifications and exercise prove to be more beneficial than either strategy on its own for alleviating symptoms of PCOD and lowering risks associated with cardiometabolic conditions. Incorporating both elements leads to more significant health improvements and supports overall well-being. In addition to nutrition and physical activity, emotional and psychological assistance is essential for women with PCOD, who face a heightened likelihood of depression, anxiety, and diminished quality of life. Programs designed with elements like cognitive-behavioral therapy, stress reduction strategies, and motivational coaching can enhance commitment to lifestyle modifications while also promoting mental health. Crucially, lifestyle changes can positively impact not just overweight or obese women but also those with PCOD who are of normal weight, enhancing insulin sensitivity and reproductive health, even when shedding pounds is not the main objective.

6.2 Pharmacological Treatment

Insulin sensitizers play a crucial role in managing Polycystic Ovarian Disease (PCOD), also referred to as Polycystic Ovary Syndrome (PCOS), especially in women with insulin resistance, a key characteristic of the condition. This resistance leads to elevated insulin levels, which further amplifies ovarian androgen production, interferes with follicle maturation, and raises the likelihood of metabolic issues, including type 2 diabetes and cardiovascular diseases.

Metformin, a biguanide drug primarily used for type 2 diabetes, is the most frequently prescribed insulin sensitizer for managing PCOD. It enhances insulin sensitivity by lowering glucose production in the liver and improving glucose absorption in tissues. Research has indicated that Metformin can help restore ovulation, normalize menstrual cycles, decrease levels of circulating androgens, and assist in weight control for women with PCOD. Furthermore, it has been found to lower the likelihood of developing impaired glucose tolerance and type 2 diabetes in this population. Overall, Metformin plays a crucial role in the effective management of PCOD symptoms and associated metabolic issues. Metformin is frequently used either on its own or alongside other therapies, such as lifestyle changes or ovulation-stimulating medications like Clomiphene Citrate, particularly in cases of anovulatory infertility in women. While Metformin is typically well-accepted, some women may encounter digestive issues. These gastrointestinal effects can usually be reduced by slowly increasing the dosage or opting for extended-release versions of the medication. In addition to Metformin, researchers have explored other insulin-sensitizing medications like Thiazolidinediones, including Pioglitazone, for the treatment of PCOD. These drugs work by stimulating the peroxisome proliferator-activated receptor-gamma (PPAR-γ), which improves insulin sensitivity in tissues such as fat, liver, and muscle. Research suggests that Thiazolidinediones can enhance both insulin sensitivity and ovulation; however, their use is restricted due to potential side effects, including weight gain, fluid retention, and possible cardiovascular complications. Hormonal therapy plays a crucial role in treating Polycystic Ovarian Disease (PCOD), especially for women exhibiting symptoms like irregular menstrual cycles and hyperandrogenism, including excessive hair growth and acne. This approach is beneficial for those not currently focused on achieving pregnancy. The main objectives of hormonal treatments are to normalize menstrual cycles, alleviate symptoms associated with elevated androgens, and safeguard against endometrial hyperplasia, a condition that may arise due to ongoing anovulation. The primary hormonal treatment recommended for PCOD is the combined oral contraceptive pill (COCP), which includes both estrogen and progestin. These pills function by inhibiting the secretion of luteinizing hormone (LH), thereby decreasing the production of ovarian androgens and increasing the levels of sex hormone-binding globulin (SHBG). This globulin binds to free androgens, reducing their bioavailability. As a result, COCPs help regulate menstrual cycles, alleviate acne, reduce hirsutism, and offer protection against endometrial disorders. They are regarded as the first-line medical option for women with PCOD who are not planning to conceive. For women who are unable to use estrogen-based contraceptives due to intolerance or contraindications, progestin-only treatments or cyclic administration of progestin may be employed to trigger withdrawal bleeding and lower the chance of developing endometrial hyperplasia. When hyperandrogenic symptoms such as excessive hair growth or acne continue to occur despite the use of combined oral contraceptive pills (COCP), it may be beneficial to introduce anti-androgen medications like spironolactone, flutamide, or finasteride. These treatments work by obstructing androgen receptors or preventing the transformation of testosterone into its more potent variant, dihydrotestosterone (DHT), thereby alleviating the intensity of symptoms linked to androgens. It is essential, however, to use these medications alongside reliable contraception due to their potential teratogenic effects. Anti-androgens are crucial in addressing Polycystic Ovarian Disease (PCOD), especially for alleviating symptoms associated

with hyperandrogenism, including excessive hair growth, acne, and hair thinning. Hyperandrogenism serves as a primary diagnostic marker for PCOD and has a considerable impact on the quality of life for numerous women affected by this disorder. Anti-androgens work by either obstructing androgen receptors, decreasing the production of androgens, or preventing the conversion of testosterone to its more active form, dihydrotestosterone (DHT). Commonly, they are combined with hormonal contraceptives, particularly for women not planning to conceive, since their standalone use may cause menstrual irregularities and pose risks of teratogenic effects.

Common Anti-Androgens Used in PCOD Treatment:

1. Spironolactone

Spironolactone is widely recognized as the leading anti-androgen medication for managing PCOD. This potassium-sparing diuretic possesses anti-androgenic effects, functioning as a competitive blocker of androgen receptors while also diminishing androgen production. Research indicates that spironolactone significantly alleviates hirsutism and acne in women suffering from PCOD. The usual prescribed dosage falls between 50 and 200 mg per day. However, owing to potential side effects such as menstrual irregularities and risks of teratogenicity, it is commonly given in conjunction with oral contraceptives to mitigate these issues.

2. Flutamide

Flutamide, a non-steroidal anti-androgen that inhibits androgen receptors, has proven effective in alleviating hirsutism and acne in females with PCOD, according to various studies. Nonetheless, concerns about its potential liver toxicity render it less preferred than spironolactone.

3. Finasteride

Finasteride works by blocking the enzyme 5-alpha-reductase, which converts testosterone into the more active dihydrotestosterone (DHT). This medication is especially useful for managing hirsutism and male-pattern baldness linked to PCOD. While it is usually well tolerated, finasteride is an anti-androgen that requires effective contraceptive measures due to its potential to cause birth defects.

4. Cyproterone Acetate

Cyproterone acetate is a progestin known for its potent anti-androgen effects. It is frequently paired with ethinylestradiol in birth control pills to treat conditions like hirsutism, acne, and irregular menstrual cycles in PCOD. Research indicates that its administration leads to notable decreases in androgen levels and improvements in hyperandrogenic symptoms.

6.3 Surgical Treatment

Surgical interventions for Polycystic Ovarian Disease (PCOD), commonly known as Polycystic Ovary Syndrome (PCOS), are typically viewed as a secondary option. This approach is mainly intended for women facing infertility due to lack of ovulation who have not had success with medical treatments for inducing ovulation. The primary surgical method employed for PCOD is laparoscopic ovarian drilling (LOD). This minimally invasive procedure aims to promote ovulation by decreasing androgen production in the ovaries and re-establishing hormonal equilibrium. LOD utilizes laparoscopic tools to repeatedly perforate the ovarian surface through methods such as electrocautery, laser, or diathermy. This technique diminishes a small segment of ovarian tissue that contributes to excessive androgen production, consequently

lowering the levels of circulating androgens and luteinizing hormone (LH). As a result, the feedback inhibition on follicle-stimulating hormone (FSH) is reduced, which encourages the growth of follicles and the process of ovulation. Numerous research studies indicate that laparoscopic ovarian drilling (LOD) is a successful method for stimulating ovulation in women suffering from polycystic ovarian disease (PCOD). Reports show ovulation rates of 50% to 80%, with pregnancy rates ranging from 30% to 60% within a year following the procedure. LOD is especially advantageous for those who do not respond to first-line treatments with clomiphene citrate, meaning they have not achieved ovulation despite using this medication.

7. Future Direction in Research

The future of exploring the genetic foundation of Polycystic Ovarian Disease (PCOD), commonly referred to as Polycystic Ovary Syndrome (PCOS), is highly promising and could enhance diagnosis, treatment, and comprehension of this intricate endocrine condition. Although the heritable nature of PCOD has been acknowledged for some time, the exact genetic processes are still not fully understood. Current research aims to clarify these complexities by employing cutting-edge genomic technologies. A significant area of future research focuses on genome-wide association studies (GWAS), which have already pinpointed several genetic loci linked to PCOD, including variants in genes such as FSHR, LHCGR, DENND1A, and THADA. Nevertheless, these identified loci account for only a small portion of the heritability associated with PCOD, indicating that there are likely more genetic influences yet to be discovered. To identify new genetic variants that may play a role in disease susceptibility, especially in diverse populations that have been underrepresented in existing studies, extensive large-scale and multi-ethnic GWAS and meta-analyses are necessary moving forward. A vital area for future exploration is epigenetics, focusing on how environmental influences can bring about inheritable changes in gene expression without modifying the DNA sequence itself. Research indicates that epigenetic alterations, including DNA methylation and histone changes, might influence the onset of PCOD by affecting genes related to steroid production, insulin pathways, and inflammation. Gaining insight into these processes could pave the way for new biomarkers for early diagnosis and innovative treatment options that extend beyond traditional methods. Additionally, advancements in whole exome sequencing (WES) and whole genome sequencing (WGS) hold significant promise. These methods enable researchers to uncover rare, impactful genetic variants associated with PCOD in particular families or individuals exhibiting severe symptoms, thus illuminating largely uncharted monogenic or oligogenic forms of the condition. Additionally, future research is anticipated to heavily rely on functional genomics and systems biology techniques. These strategies focus on combining genetic, transcriptomic, proteomic, and metabolomic information to develop detailed models of the pathophysiology associated with PCOD. By employing these integrative methods, researchers could uncover essential regulatory networks and pathways related to the disease, potentially paving the way for more precise and tailored treatment options. Upcoming studies will probably investigate the interplay between genetic and environmental factors that influence PCOD, focusing on the ways genetic predisposition interacts with elements like nutrition, obesity, exposure to endocrine disruptors, and stress. Gaining insight into these relationships may facilitate the development of preventive measures and early intervention tactics,

particularly for those who have a familial background of PCOD.

8. CONCLUSION

Polycystic Ovarian Disease (PCOD), widely recognized as Polycystic Ovary Syndrome (PCOS), is a complex endocrine disorder impacting a considerable number of women of reproductive age globally. The causes of this condition are multifactorial, involving a mix of genetic, hormonal, metabolic, and environmental influences. Key components in its development include insulin resistance, hyperandrogenism, and ovarian dysfunction, with chronic inflammation, oxidative stress, and abnormalities in adipose tissue further exacerbating the disease. The symptoms of PCOD vary widely and may include irregular menstrual cycles, anovulation, infertility, hirsutism, acne, hair loss, obesity, and metabolic issues such as dyslipidemia, which increases the likelihood of type 2 diabetes and cardiovascular problems. The Rotterdam criteria, which incorporate clinical, biochemical, and ultrasound assessments, are the most commonly used guidelines for diagnosing PCOD. Management of PCOD is tailored to the individual and focuses on alleviating specific symptoms. A foundational aspect of treatment involves lifestyle changes, such as weight control, dietary modifications, and enhanced physical activity. Depending on the patient's symptoms and reproductive objectives, medical treatments might include insulin sensitizers like Metformin, hormonal therapies such as birth control pills, anti-androgens like Spironolactone, and ovulation stimulants like Letrozole. In certain circumstances, surgical approaches like laparoscopic ovarian drilling could also be an option. Recent studies emphasize the significance of exploring the genetic aspects of PCOD, with genome-wide association studies (GWAS) identifying potential genes linked to the disorder's development, which could lead to future advancements in personalized medicine.

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