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Polycystic Ovary Syndrome (PCOS): A Concerning Hormonal Condition and its Bodily Impact on Women

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Abstract

Polycystic Ovary Syndrome (PCOS) is a prevalent hormonal disorder that have severe health consequences for women. It arises in the early puberty stage and affects a large percentage of the world's population. While the exact cause is unknown, it's known to cause hyperandrogenism, insulin resistance, menstrual irregularities, and ovulatory dysfunction, all of which can lead to infertility and endometrial cancer. Long-term cardiometabolic risks and comorbidities are seen in both slim and obese PCOS patients. Given these serious implications, it's critical to fully comprehend the pathophysiological relationships that underpin PCOS, so that better treatment plans can be developed and the standard of living for women having this condition may improve. This condition is diagnosed using three separate criteria. Rotterdam criterion is mostly utilized for PCOS diagnosis. Different symptoms of PCOS are treated in different ways. It's imperative to comprehensively treat these patients as soon as possible in order to cope with the emotion burden associated with the disease that is often ignored. PCOS can be managed by early diagnosis and long-term treatment, allowing women to maintain a healthy lifestyle and avoiding long-term complications, including metabolic syndrome and cardiovascular diseases.

1. Introduction

Polycystic ovary syndrome (PCOS) is a serious disorder marked by hyperandrogenism, irregular menstruation cycle, and possibly small cysts in the ovaries [1]. It is described as a disease in which one or both ovaries produce an estimated 10 small cysts measuring 2-9 mm in diameter and ovarian volume in one or both ovaries reaching to 10 ml [2]. PCOS is a hormonally imbalanced endocrine and metabolic condition characterized by hyperandrogenic symptoms that have both short- and long-term health concerns for women [1]. Hyperandrogenism, insulin resistance, and chronic anovulation are all symptoms of PCOS, and 6-20% of women of reproductive age are affected by it [3]. It's a diverse disorder with unknown etiologies that are linked to the complex association of metabolic, endocrine, genetic, and environmental variables. Substantial studies indicated that in both overweight and lean PCOS patients, insulin resistance (IR), and secondary hyperinsulinemia serve as a crucial cooperative part in the production and

sustaining of metabolic changes and anovulation with hyperandrogenism [4]. It is considered to be the leading cause of infertility [5]. Furthermore, it has been linked to unfavourable health conditions, such as reproductive (irregular menstruation, infertility) [1], metabolic (IR, diabetes mellitus, cardiovascular disease risk), and psychological (anxiety, depression) complications [6]. Being overweight has been described as a major issue for PCOS patients, especially teenagers [7]. Hirsutism affected nearly 70% of PCOS patients, and they usually stated it as one of the most distressing features of PCOS [8]. National Institutes of Health (NIH) diagnostic criteria, systematic screening of women reported that 4-10% of reproductive-age women have PCOS [2]. Latest studies indicated that PCOS is a chronic condition that manifests from prenatal age, even though it was historically regarded as a disease of adult women. However, the disease's incidence in children is still uncertain [2]. Incidence of disorder varies based on the diagnostic criteria used, ranging from 6% (using the NIH criteria)-18% (by Rotterdam criteria) of reproductive-age women of various ethnicities [9]. In contrast, patients without PCOS, patients are twice likely to be hospitalized due to reproductive issues like infertility and non-reproductive issues like type II diabetes, heart disease, circulatory disorders, musculoskeletal system disorder, mental health issues, and cervical cancer diagnosis [2]. Therefore, precise and timely identification of PCOS is important not just to avoid possible health complications but also to reduce economic costs and burden [2].

The current review summarizes recent and pertinent PCOS studies. The aetiology, pathophysiology, clinical features, and diagnostic criteria of this disease were also briefly discussed in the current research. In addition, morbidities associated with PCOS and their effects on the body of females are also discussed and included, while underlying details on the different treatments and regimens for women living with this disorder. The current study also discusses the environmental factors and complications associated with this disorder/chronic disease.

2. Materials and Methods

The previous literature review was reviewed by using different search engines of the database, (PubMed, CrossRef, Publisher Site, CAS, and Google Scholar). Data were included from research articles (2000-2021). The research articles were searched by using various key terms: Polycystic Ovary Syndrome, hyperandrogenism, aetiology, pathophysiology, the clinical presentation of PCOS, effects of PCOS on the female bodies, long-term health consequences of PCOS, diagnostic criteria of PCOS, and treatments for PCOS using Google search engine.

2.1. Aetiology of PCOS

2.1.1. Insulin Resistance and Hyperandrogenism

Since there is no single cause of polycystic ovary syndrome, the most widely recognized assumption is a multivariate model in which associations among environmental indicators and factors specific to each person result in a common outcome. This results in the production of hyperandrogenemia, a biochemical marker of disease. The key malefactor behind PCOS clinical manifestations is this specific modification of insulin resistance [4]. Other factors contributing to PCOS aetiology include obesity, ovarian dysfunction, and hypothalamic-pituitary

defects, along with other genetic and environmental factors [1]. Hyperandrogenism is a condition induced by extravagant androgen development and secretion, and is characterized by acne, hirsutism, or frontal alopecia. Hyperandrogenemia is characterized as an enhanced androgen level in the blood [4]. Hyperandrogenism is a well-known cause of the aetiology of PCOS, accounting for 50-80% of cases [10]. Insulin resistance (IR) is a metabolic state in which a cell's ability to act to insulin signalling declines and appears as a key pathophysiological factor in all PCOS-related metabolic abnormalities [11]. IR is caused by impaired insulin function in glucose uptake and utilization [12]. It's a pathophysiological benefactor in approximately 60-80% of PCOS patients [10]. Ovarian activity is disrupted and androgen levels are increased as a result of IR and its raised level which contributes to anovulation [13]. Gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin levels are also affected in PCOS cases [12].

2.1.2. Genetic Factors

Genetic factors have a significant role in PCOS aetiology, in addition to environmental factors. In its cause candidate genes, SNPs (Single Nucleotide Polymorphisms) are involved. The aetiology of PCOS, according to databases, includes 241 gene variants [14]. Polymorphisms or nucleotide changes induce a defect in a gene's transcriptional activity which leads to PCOS. The majority of the genes encoding for the androgen receptor, LH receptors, FSH receptors, and leptin receptors are to blame [15]. A genetic abnormality disrupts the metabolic mechanism, resulting in ovarian dysfunction, steroidogenic acute regulatory (StAR), follicle-stimulating hormone receptor (FSHR) and fat mass or obesity-associated (FTO) gene polymorphisms, vitamin D-receptor (VDR) polymorphisms, insulin receptor (IR) and IR substrate (IRS) polymorphisms, and gonadotropin-releasing hormone receptor (GnRHR) gene polymorphisms, have been linked to PCOS [16]. The progression and severity of PCOS get worse with the rise of insulin and androgen levels. Theca cells of the ovary are affected by hyperinsulinemia which raises the androgen levels. SHBG and IGFBP-1 production in the liver reduce as a result of this disease. On the other hand, higher androgen level encourages the production of free fatty acids (FFAs) in visceral adipose tissue (VAT) which contributes to insulin resistance [15].

A link has been discovered between 'pro-inflammatory' genotypes and polycystic ovarian syndrome, connected to polymorphisms in genes coding for tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), and interleukin-6 receptors. The discovery of abnormal early gonadotropin-independent folliculogenesis in PCOS patients revealed that genes linked to folliculogenesis might be contenders for the etiology and pathogenesis of this condition [17].

Genetic factors play a vital role in the progression of this syndrome by laying the groundwork for unusually elevated androgen production in ovary tissue [18]. A widely accepted model predicts the Mendelian pattern of inheritance in which major genetic abnormalities are passed onto offspring in a dominant autosomal fashion but with vastly varying penetration depending on a variety of environmental and epigenetic influences, like utero exposure to high androgen levels [18].

Enhanced androgen production was found in PCOS women's ovarian theca cells due to the increased ovarian steroidogenesis which was linked to altered expression of key enzymes (Cytochrome P450 enzymes: CYP17, CYP21, CYP19, and CYP11A) in the steroid hormone biosynthesis pathway [19]. In addition, other cytogenetic anomalies, the association between PCOS and X-chromosome aneuploidies and polyploidies have been confirmed. A hypothesis stated that X chromosomal factors producing an irregular follicular apparatus could be responsible for at least some cases of PCOS [20]. The AR gene (Androgen Receptor gene) is found on the "q" arm of chromosome X. Gene mutations and structural disturbances are thought to be the causes of polycystic ovary syndrome. The biological mechanism is disrupted when the "X" chromosome is inactivated, leading to an increase in the androgen hormone and polycystic ovary syndrome [21]. PCOS aetiology including genetic, metabolic, psychological, and reproductive issues are mentioned in Figure 1.

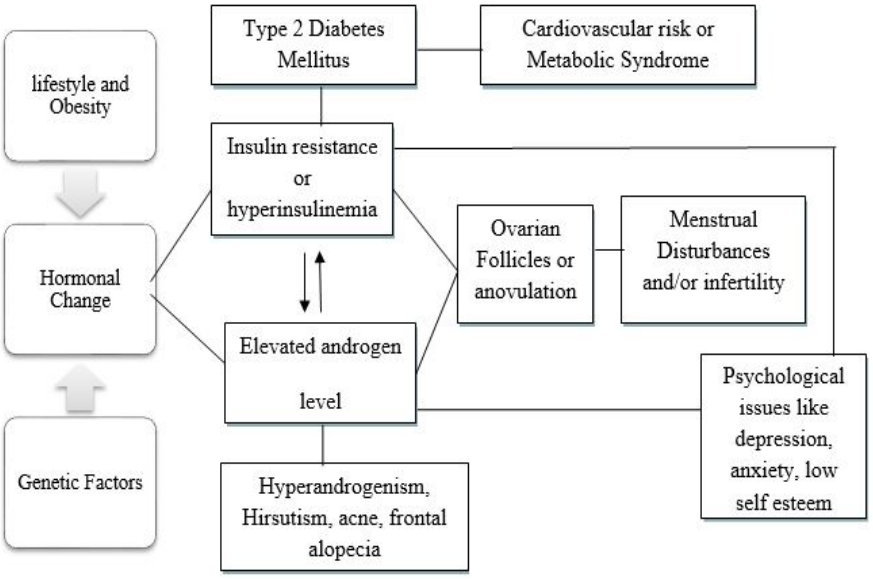

Figure 1. PCOS Aetiology including Genetic, Metabolic, Psychological and Reproductive Issues

2.2. Pathophysiology of PCOS

PCOS pathophysiology includes main abnormalities in the hypothalamic-pituitary axis, insulin release and its functions along with ovarian activity [22]. Though the origin of PCOS is unidentified and has been associated with IR and obesity. Insulin is linked to insulin function; insulin helps in the regulation of ovarian activity and ovaries react to excessive insulin by releasing androgens that cause anovulation [13]. Insulin causes biochemical and clinical hyperandrogenism by directly increasing the development of theca cell ovarian androgen with luteinizing hormone

(LH) [3] and indirectly by reducing sex hormone-binding globulin (SHBG), carrier protein that decreases the level of free circulating testosterone [23]. Previous studies stated that the production of testosterone, progesterone, and 17-hydroxyprogesterone by theca cells are elevated in PCOS patients than in controls. These cells have been altered in PCOS patients with high amounts of cytochrome P450 (CYP) 11A, 3-HSD2, and CYP17 genes [24]. Clinical markers of PCOS include elevated levels of LH and GnRH, as well as unchanged levels of FSH. In return, as gonadotropin-releasing hormone level increases, theca cells of ovaries are stimulated and release more androgens [18]. Follicular maturation arrest indicates an ovarian defect. The follicular arrest may be reversed by raising the levels of endogenous FSH or by supplying exogenous FSH [4]. Around 25% of PCOS patients have elevated prolactin levels [24]. PCOS reflects the interactions between epigenetic and environmental factors mediated by multiple proteins and genes [1] (Figure 2).

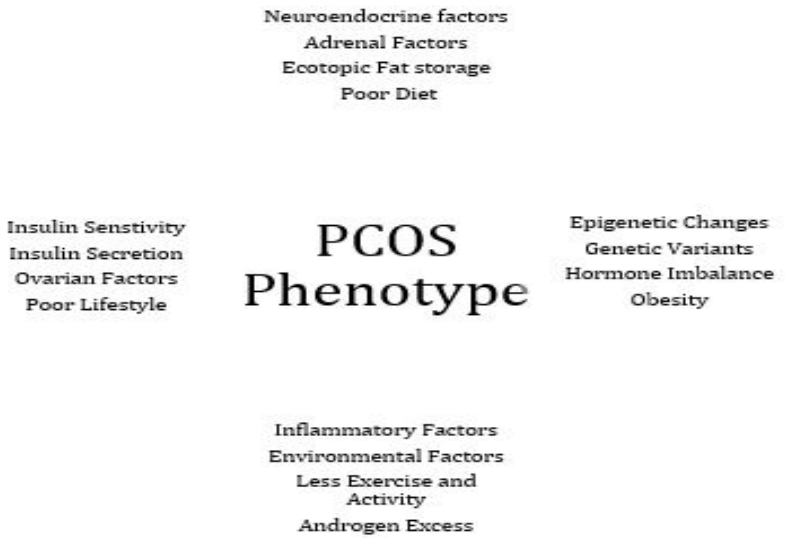

Figure 2. Factors Contributing PCOS Phenotype

2.3. Signs and Symptoms

PCOS complexity isn't due to its name; it's because it's linked to a slew of other issues. In the sac of their ovary, PCOS patients develop >12 cysts with a diameter of 8 mm. Due to this disease, around 70% of females are infertile [15]. In PCOS androgen level is increased and it results in hirsutism and acne. Insulin resistance in PCOS results in obesity and type II diabetes. This issue causes irregularities in the menstrual cycle which leads to infertility. Sleep apnea affects 20% of females regularly. Anxiety and depression are very frequent [25] (Figure 3). Comprehensive physical check-ups, anamnesis of patients, and lab tests must be carried out for accurate diagnosis and timely treatments [1].

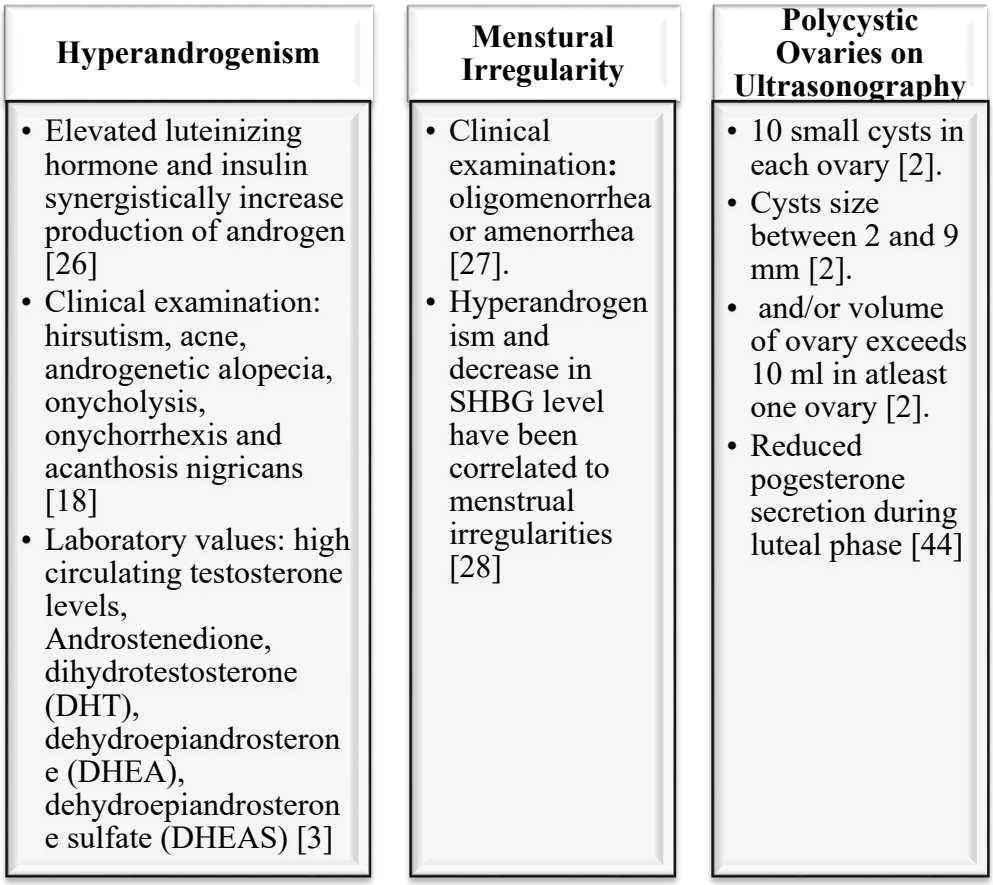

Figure 3. Signs and Symptoms of PCOS Patients

2.4. Diagnosis

Three separate sets of guidelines have been used to diagnose PCOS over the last twenty years. In 1990, the National Institutes of Child Health and Human Development (NICHD) published NIH criteria; in 2003, the PCOS consensus meeting accepted the Rotterdam criteria, and in 2006, the Androgen Excess (AE) and the PCOS Society (AE-PCOS) criteria was suggested [30]. Table 1 shows the PCOS diagnostic criteria in detail.

Table 1. PCOS Diagnostic Criteria

National Institutes of Health (NIH) 1990	Rotterdam criteria developed by the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM) 2003	Androgen Excess and PCOS Culture (AE-PCOS)

1999 criteria	**Revised 2003 criteria**	**2006criteria**
Include the following parameters [30] 1.Oligo/amenorrhea Anovulation 2.Clinical and/ or biochemical signs of hyperandrogenism, and exclusion of other aetiologies (non-classical congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, drug-induced androgen excess, severe IR syndrome, thyroid dysfunction, hyperprolactinaemia) with/without PCOS on ultrasound	Accepts two out of the following three parameters [30] 1.Oligomenorrhea and/ or anovulation 2.Clinical and/ or biochemical signs of hyperandrogenism 3.Polycystic Ovaries (by ultrasound) and exclusion of other aetiologies (non-classical congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, drug-induced androgen excess, severe IR syndrome, thyroid dysfunction, hyperprolactinaemia)	Recommends diagnosis in the presence of the following parameters [30] 1. Clinical and/ or biochemical signs of hyperandrogenism 2.Either Ovarian dysfunction or Polycystic Ovaries and exclusion of other aetiologies (non-classical congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, drug-induced androgen level increase, severe IR syndrome, thyroid dysfunction, hyperprolactinaemia)

A variety of PCOS phenotypes are produced by various diagnostic criteria. Even before the Rotterdam criteria was accepted there were different PCOS subgroups that differ metabolically. The NIH Consensus Panel in 2012, suggested a phenotypic approach to classify PCOS [31]. Phenotypes of PCOS were divided into four diagnostic groups for simplification as summarized in Table 2.

Table 2. Diagnostic Phenotypes of PCOS

Phenotype A	Full-blown PCOS: clinical/biochemical hyperandrogenism (HA), oligo-/anovulation (OA) and polycystic ovarian morphology (PCOM)
Phenotype B	Non-PCO PCOS: clinical/biochemical hyperandrogenism (HA), oligo-/anovulation (OA)
Phenotype C	Ovulatory PCOS: clinical/biochemical hyperandrogenism (HA), and polycystic ovarian morphology (PCOM). Ovulation is normal
Phenotype D	Non-hyperandrogenic PCOS: no hyperandrogenism, but oligo/anovulation occurs with PCOS

The basic criteria to be considered for the diagnosis of PCOS is levels of FSH, LH, and androgen. Increased luteinizing hormone level contributes to raising the level of androgen that leads to PCOS progression [32]. Following the diagnosis of PCOS, a comprehensive health examination must be performed so that the physician could learn about unusual gain in weight, menstruation irregularities, male pattern hair development, skin variations, and high blood pressure from the patient's medical history and physical examination. A blood sample was taken to monitor the level of hormones, glucose, and lipid in the patient's body, as well as pelvis ultrasonography, for checking cysts in ovaries [32]. Other possible causes of reproductive, endocrine, and metabolic dysfunction must be omitted during the evaluation process. Doctors must exclude hyperprolactinemia, adrenal hyperplasia, and Cushing's syndrome before diagnosing polycystic ovary syndrome [32]. More than half of the PCOS patients experience prediabetes or diabetes after diagnosis, according to the previous research, and a higher possibility of myocardial infarction (MI), hypertension, anxiety or depression, dyslipidemia, endometrial cancer, and sleep apnea [33]. Pregnant women with PCOS must be warned about the elevated risk of abortion, gestational diabetes,

preeclampsia as well as early childbirth [34].

2.5. Effects of PCOS on Female Bodies

2.5.1. Hirsutism

Patients also refer to hirsutism as one of the most troubling aspects of PCOS and it can put a lot of emotional strain on the patient [35]. Hirsutism is a condition in which females develop excessive hair on their faces and bodies in a male-like shape [3]. Hirsutism is caused by an increase in circulating free testosterone which causes the pilosebaceous unit to convert vellus hair to terminal hair [23]. Thus, hirsutism is a product of hyperandrogenism and effects the hair follicle unit [3]. PCOS is the most prevalent cause of high androgen levels, with 60–80% of PCOS women experiencing hirsutism [36]. In addition, the modified Ferriman Gallwey scale was most widely used to assess hirsutism which measured the quantity of hair growth on numerous androgen-dependent body locations. However, race and ethnicity, have an important role in hirsutism [23]. PCOS patients with hirsutism often express feelings of being unfeminine, freakish, weird, and being different [35].

2.5.2. Acne and Seborrhoea

Sebaceous glands (androgen-dependent structures) contain sebocytes which are very susceptible to androgen signalling and result in acne and seborrhoea [37]. Acne is caused by the formation of comedones as a result of the aggregation of sebum and decayed epithelial follicular cells which allows the Propionibacterium acne bacterium to colonize [38]. In the areas of the face like the forehead, mid-back, and chin, androgens stimulate sebocytes proliferation and sebum secretion [37]. Sebum is a combination of different lipids that include glycerides, squalene, free fatty acids (FFA), cholesterol, cholesterol esters, and wax esters [39]. It becomes even more complicated because local bacteria secrete lipolytic enzymes and it breaks down the triglycerides formed within sebocytes [37]. Whereas androgen levels are higher in acne-prone women, acne has not been attributed to any specific hormone, except for the adrenal androgen Dehydroepiandrosterone-Sulfate (DHEA-S), total testosterone, and free testosterone [38].

2.6. Associated Morbidities and their Impact on Diseased women

2.6.1. Obesity: A Key Factor of PCOS

Obesity is known as one of the most critical PCOS characteristics. In diseased women, its prevalence ranges from 61-76%. Obesity increases the chance of getting PCOS [2]. In transmitting metabolic characteristics of PCOS, obesity plays a significant role. PCOS patients have an atherogenic lipid profile which includes high low-density lipoprotein levels, triglycerides, and cholesterol, as well as, low high-density lipoprotein levels. Atherosclerosis, arterial stiffness, and altered endothelial vascular function are all more likely in them [2]. Obesity increases androgen production by activating LH, resulting in hyperandrogenism [40]. Obese PCOS patients are more likely to experience anovulation and, as a result, subfertility [24]. Furthermore, obesity causes hyperinsulinemia by decreasing insulin metabolism and elevating insulin production, as well as, influencing insulin clearance through serum androgens [26].

2.6.2. Ovarian Dysfunction and Infertility

Hormone imbalances in women can induce menstrual irregularities such as oligomenorrhea, amenorrhea, and

anovulation which could lead to ovarian dysfunction, uterine bleeding, and infertility [37]. Follicle growth is disrupted in PCOS patients because of high androgen levels in ovaries, IR-induced hyperinsulinemia, and intra-ovarian paracrine signalling. Hyperinsulinemia slows follicle growth and raises serum-free testosterone levels. Excess insulin also promotes premature follicle luteinization. In tiny PCOS follicles, an excess of anti-Müllerian hormone (AMH) produced by granulosa cells of ovarian follicles seems to oppose follicle-stimulating hormone action. Follicular arrest development in the ovary is aided by reduced follicle-stimulating hormone levels which results in amenorrhea, anovulation, and polycystic morphology [41]. According to various studies, the incidence of oligomenorrhea has risen significantly in the past few decades, ranging from 12-15.3%, with 10-20% of infertile women experiencing it [42]. Amenorrhea is defined as an inability of the hypothalamic-pituitary-gonadal axis to cause periodic alternations in the endometrium which would ordinarily lead to menstruation [43]. In PCOS, primary or secondary amenorrhea is caused by the silent effects of elevated androgen levels on gonadotropin-releasing hormone secretion that results in elevated luteinizing hormone secretion. Several neurotransmitters related to PCOS pathophysiologies, like neurokinin B and dynorphins, affect LH activity [44]. In teenagers with PCOS, the incidence of the irregular menstrual cycle appears to differ considerably: roughly 43% have oligomenorrhea, 21% have primary/secondary amenorrhea, and 21% have menstruation, while 7% have polymenorrhea. Amenorrhea affects 95% of adult polycystic ovary syndrome patients [45]. Approximately 80% of women with anovulatory infertility suffer from PCOS which is exacerbated by obesity. Furthermore, anovulatory infertility causes a longer interval between ovulation and conception, women with anovulatory infertility are more likely to require fertility testing and treatment [34]. A number of studies have revealed that PCOS-affected females face pregnancy-related problems such as gestational diabetes, hypertension due to pregnancy, pre-eclampsia, and a higher possibility of abortion [2]. In terms of the impact on the foetus, affected females are 2.5 times more likely to give birth to small children of gestational age than control groups, and their offspring have higher morbidity and mortality rate relative to controls [2]. Other conditions that affect females during PCOS are given in Table 3.

Table 3. Conditions Affecting Females during PCOS

Androgenic Alopecia	Androgenic alopecia is patterned slow hair loss caused by increased androgen concentrations and secretions. Testosterone converts into dihydrotestosterone (DHT) in sensitive hair follicles, resulting in elevated DHT levels that bind to androgen receptors and genes responsible for the progressive transformation of big terminal follicles. The hormone receptor activates the miniaturized follicles [37].
Dyslipidemia	Disorder of dyslipidemia is characterized by an abnormal lipid profile, which may include raised levels of plasma cholesterol, triglycerides, or both, or lower High-Density Lipoprotein Cholesterol (HDL-C) levels. Women suffering from PCOS have abnormal lipid levels and dyslipidemia is one of the most common symptoms of PCOS [46].

Cardiovascular disease risk	Women with PCOS are more likely to have risk factors for cardiovascular disease (CVD), which are primarily mediated by insulin resistance, as well as hormonal and metabolic processes. Research has revealed that women with PCOS are more likely to have higher subclinical CVD markers like coronary artery calcium scores, C-reactive protein, carotid intima-media thickness, and endothelial dysfunction [47].
Endometrial Cancer	Chronic anovulation in women with PCOS causes unopposed exposure to uterine estrogen and a lack of progesterone activity. This can then lead to endometrial hyperplasia and eventually to endometrial cancer [48].
Oncholysis and Onychorrhexis	Hyperandrogenism in PCOS aggravates oncholysis and onychorrhexis. Oncholysis occurs when the onychodermal band is disrupted, causing the nail plate to separate from the nail bed, and onychorrhexis, or the breaking of nails in longitudinal bridges is also a possible consequence of PCOS [37].
Acanthosis Nigricans	Acanthosis nigricans is dark, pigmented skin that occurs on the nape of the neck, axilla, underarms, inner thigh and groin area due to insulin resistance and hyperandrogenism. High insulin levels either directly or indirectly stimulate the insulin-like growth factor receptor (IGFR) on the ovary, causing high androgen production and skin changes [26].

2.7. Psychological Features of PCOS

Obesity, acne, hirsutism, and irregular menstrual cycles are all linked to PCOS and they add significantly, to the patient's psychological burden due to sexual dysfunction and issues with feminine identity and body image [49]. To date, limited research showed that PCOS patients are susceptible to eating disorders, depression, anxiety, low self-esteem, negative body image, and psychosexual dysfunction [50]. Psychosexual dysfunction appears to be more common in PCOS, ranging from 13.3-62.5%, which appears to be higher than the general population's prevalence. [50]. One of the most prevalent psychological disorders linked to polycystic ovary syndrome is depression. According to studies conducted around the world, the prevalence of depression in PCOS ranges from 23-64%. Anxiety disorders are estimated to affect 11.5-38.6% of PCOS patients [51].

2.8. Long-term Health Consequences of PCOS

2.8.1. Cardiovascular Disease Risk

Polycystic ovary syndrome patients have a greater prevalence of cardiovascular disease (CVD) risk factors, which tend to cluster together. With a prevalence of up to 15%, this syndrome is a frequent endocrine illness among reproductive-age women [52]. Polycystic ovary syndrome is associated with cardiometabolic abnormalities like obesity, dyslipidemia, Diabetes Mellitus Type 2, hypertension, and metabolic syndrome, all of which raise the risk of cardiac disease [52]. PCOS patients have a greater risk of coronary heart disease (CHD) and stroke relative to controls, according to previous research and meta-analyses [47]. While several researchers have found that this association is independent of BMI, others have suggested that traditional cardiovascular disease risk factors might explain this increased CVD risk and that PCOS's

absolute risk might be minimal [47]. Besides IR, metabolic syndrome, impaired glucose tolerance, and Diabetes Mellitus Type 2 also have elevated levels in women with PCOS [47]. There is a scarcity of long-term anticipated research that's why the risk of CHD or stroke in affected females remains unknown. More recent results showed that PCOS patients have higher carotid intima-media thickness and coronary artery calcification, two significant surrogate indicators for atherosclerotic CVD. PCOS patients showed considerably higher levels of CVD circulating biomarkers, such as C-reactive protein [41].

2.8.2. Endometrial Cancer

Chronic anovulation exposes the endometrium to unopposed uterine estrogen which can lead to endometrial hyperplasia and, ultimately, to endometrial cancer [48]. Obesity, long-term usage of unopposed estrogen, nulliparity, infertility, hypertension, and diabetes are all known variables that raise the risk of endometrial cancer. Majority of these factors have been linked to PCOS [53]. Polycystic ovary syndrome patients had a 2.7 times greater risk of endometrial cancer relative to controls, with a lifetime risk of up to 9% in women with the syndrome [54]. The correlation between PCOS and endometrial cancer is still unknown [55].

2.8.3. Ovarian Cancer

PCOS has been studied as a potential cause of ovarian cancer in several studies but the results have been conflicting. However, in some studies, oligomenorrhea has been linked to the elevated potential cause of ovarian cancer [56]. Hormonal changes in females having oligomenorrhea, particularly raise androgen levels, a typical feature of PCOS patients, have been proposed as a potential reason for the higher risk of ovarian cancer. However, ovarian cancer histotypes have rarely studied these connections which could explain the absence of apparent correlations described in prior research [56]. Various studies suggested that PCOS raises the risk of ovarian cancer by increasing androgen exposure. Androgen receptors are found on both benign and borderline tumors as well as in normal ovarian cells. Additionally, doubling androgen levels during pregnancy is linked to a 40–50% higher chance of developing borderline serous and invasive mucinous tumors [57]. Given that serous borderline tumours have higher levels of androgen receptors than serous invasive tumours. Moreover, it is possible that women with PCOS have an increased risk of developing the borderline serous subtype of ovarian cancer. This suggestion supports the idea that androgens may play a role in the development of ovarian cancer [58].

2.8.4. Breast Cancer

PCOS symptoms and consequences have previously been linked to both higher as well as to lower risks of developing breast cancer. Previous studies found that obesity has raised breast cancer potential in postmenopausal women, while reducing the risk in premenopausal women but infertility caused by ovulation issues has reduced breast cancer risk [58]. However, no research has yet discovered a relationship between polycystic ovary syndrome and the risk of developing breast cancer [58].

2.9. Treatments

There are numerous PCOS treatments available. Lifestyle changes like healthy food, workout, as well as losing weight are considered critical and are regarded as the first line of treatment for polycystic ovary syndrome [24]. Foods having fewer carbs and a lower glycemic load are advised.

Women with PCOS must also exercise three times per week for at least 30 minutes of moderate activity. Losing 10% of one's body weight may aid in the regularisation and predictability of one's menstrual cycle. Women with PCOS who lose weight may find it easier to conceive [24]. According to various studies, it is stated that increasing vitamin D intake is beneficial for reducing adverse effects in PCOS patients since it lowers the level of testosterone and maintains inflammatory markers such as C-reactive protein, and reduces oxidative stress. In addition to weight management, a multivitamin that contains Vitamin B12, zinc, magnesium, and folate is recommended. It's also important to drink plenty of water during the day and get enough sleep [24].

In cases of hirsutism, cosmetic therapy combined with oral contraceptive pills (OCPs) is indicated, it needs 6-9 months to show results because the hair growth cycle is typical of 6 months. Only after 6 months of OCPs anti-androgen should be introduced if necessary [59]. Topical drugs like 13.9% eflornithine cream treat mild hirsutism on the face in females having mild skin irritability [1]. Due to its diverse nature, PCOS does not have a consistent treatment. However, lifestyle changes, hormonal contraception, and other medicines such as inositol, clomiphene, eflornithine, finasteride, flutamide, letrozole, metformin, and spironolactone are effective in treating symptoms of polycystic ovary syndrome [5]. By repressing the hypothalamic-pituitary-ovary axis, OCP reduces LH secretions, increases Sex Hormone Binding Globulin levels, and decreases free testosterone levels. This fixes hyperandrogen-mediated symptoms that boost acne and hirsutism, corrects menstrual irregularities, and offers mean of successful birth control. To achieve satisfactory results against acne and hirsutism, OCP treatment should be continued for at least 6 months [2]. Patients with PCOS and acne who are unable to use OCPs may benefit from just isotretinoin treatment [60]. Alopecia is treated with OCPs and androgen blockers, however, there is little evidence to determine their exact efficiency. Topical minoxidil is recommended as first-line therapy [59].

Oral contraceptives are commonly used to treat menstrual problems. In the case of menstrual abnormalities, spironolactone, acarbose, rosiglitazone, and metformin were found to be beneficial [37]. Metformin has been effective to ameliorate IR in women with polycystic ovary syndrome and it is considered a first-line treatment for insulin resistance or glucose intolerance. Rosiglitazone and pioglitazone have shown positive results in treating symptoms of PCOS [37]. Clomiphene citrate (CC) is most effective for treating anovulatory infertile women. Through a negative feedback mechanism, CC raises FSH levels by blocking the estrogen receptor. Tamoxifen works in the same way as clomiphene to treat anovulation in those patients who are unable to respond to CC [40]. For anovulatory infertile PCOS women, gonadotropins like recombinant follicle-stimulating hormone and human menopausal gonadotropin (HMG) are second-line therapy options. In PCOS patients, low-dose follicle-stimulating hormone treatment is effective in inducing ovulation and improving the rate of conception. For clomiphene-resistant PCOS women or non-responders to clomiphene, laparoscopic surgery is a second-line surgical technique for ovulation. Laparoscopic Ovarian Drilling (LOD) is a procedure in which the ovary is ruptured several times with a laser or diathermy. In-vitro fertilization (IVF) is

indicated as a third-line treatment option for PCOS women with infertility who do not have any associated problems [40].

Figure 4 shows the targeted approach in the therapy of Polycystic Ovary Syndrome.

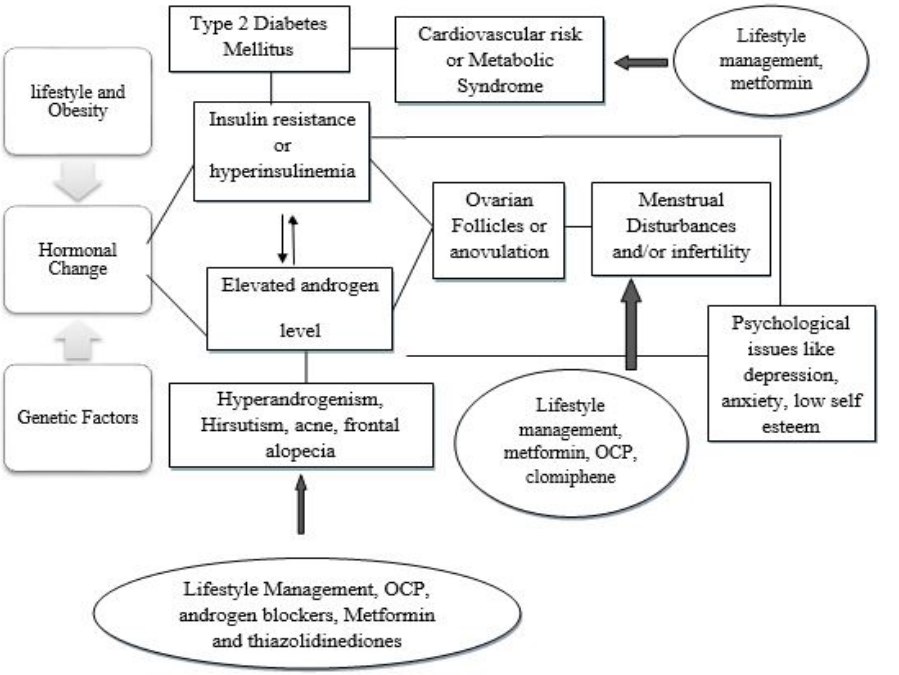

Figure 4. Targeted Approach in Therapy of Polycystic Ovary Syndrome

3. Discussion

PCOS is a common heterogeneous endocrine disorder in females and has reproductive, metabolic, and psychological characteristics. It's a chronic condition with life-long symptoms and a huge health and economic burden [2]. PCOS is becoming more prevalent in women of reproductive age and has long-term consequences. The pathophysiology of this disorder leads to both hyperandrogenism and insulin resistance. Insulin resistance occurs particularly in obese PCOS patients and they are at a higher risk of metabolic syndrome, prediabetes, and diabetes type 2 [41]. The ambiguity of its diagnosis criteria and the complexity of its characteristics are two of the most difficult aspects of this condition. Division of phenotypes allows us to better understand PCOS pathophysiology and can also help to predict adverse metabolic and cardiovascular outcomes [31]. The severity of this disorder is emphasized by morbidities as it affects multiple body systems, whether endocrine, gynecological, cardiac, or psychological. Researchers and health practitioners must follow the generally accepted diagnostic criteria [2]. Delays in treatment can cause other health problems in patients such as metabolic syndrome and cardiovascular disease. Obesity being a general feature of PCOS

can exacerbate many of the reproductive and metabolic symptoms [41]. For the management of this disorder the only way is the early identification of long-term morbidities by effective screening tests. Lifestyle improvements are highly recommended as a vital part of management [24]. OCPs are the key anovulation and hyperandrogenism medicine of choice; clomiphene citrate is recommended dose for infertility. Furthermore, research in genetics and the pathophysiology of PCOS is required to identify both preventive risk factors and effective treatment options for PCOS [2].

3.1. Conclusion

PCOS is a widespread reproductive and metabolic disorder with various phenotypes and unexplained underlying pathophysiology. Aside from the environmental factors, several potential genes have been linked to PCOS and ovarian dysfunction. The immensity can only be decreased if adequate precautionary steps are followed, for instance, weight loss, lifestyle management, and prescribed treatments. Therefore, therapies concerning PCOS focuses on symptoms control (anovulation-induced infertility, obesity, and hirsutism) and the avoidance of long-lasting health complications (endometrial cancer, type 2 diabetes). PCOS diagnostic standards are constantly evolving, and novel therapeutic approaches are being tested on regular basis. To include adequate counselling, screening, and management options, all professionals involved in the multidimensional treatment of PCOS patients must be aware of their long-term health concerns. There are still missing blocks in the knowledge provided by different researches. More researches should be conducted on this prevailing disease so that appropriate treatments should be facilitated to the females suffering from it. Furthermore, researches must focus on the pathophysiology of this disorder so that physicians would be able to treat symptoms related to PCOS.

Conflict of interests

The authors declare no conflict of interest.

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