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Review Article

Cardiovascular Risks in Women with Polycystic Ovary Syndrome (PCOS): A Narrative Review

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Received date: June 02, 2025; **Accepted date:** June 24, 2025; **Published date:** July 02, 2025

Citation: Zeinab Habibi, Armina Torabian, Kosar Sabzpoosh, Fateme Ansari, Fatemeh Afkhami, et al, (2025), Cardiovascular Risks in Women with Polycystic Ovary Syndrome (PCOS): A Narrative Review, *J Clinical Research and Reports*, 20(2); **DOI:**10.31579/2690-1919/542

Abstract

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disease affecting women of reproductive age, with global prevalence estimates ranging from 5% to 20%. It is hallmarked by hyperandrogenism, oligo-ovulation or anovulation, and polycystic ovarian morphology PCOS also presents with additional signs and symptoms, such as obesity, infertility, acne, complications of pregnancy, insulin resistance, hirsutism, androgenic alopecia, and mood disorders. While cardiovascular disease (CVD) is the leading cause of mortality worldwide for both women and men.

Keywords: cardiovascular disease (cvd; polycystic ovary syndrome(pcos); cardiometabolic risk; hyperandrogenism; metabolic syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrine disease affecting women of reproductive age, with global prevalence estimates ranging from 5% to 20%. It is hallmarked by hyperandrogenism, oligo-ovulation or anovulation, and polycystic ovarian morphology [1,2] PCOS also presents with additional signs and symptoms, such as obesity, infertility, acne, complications of pregnancy, insulin resistance, hirsutism, androgenic alopecia, and mood disorders [3]. While cardiovascular disease (CVD) is the leading cause of mortality worldwide for both women and men [4]. PCOS is linked to a variety of detrimental cardiometabolic risk factors, such as obesity, insulin resistance (IR), dysregulated glucose and lipid metabolism, hypertension, and metabolic syndrome, all of which are associated with an elevated risk for future cardiovascular events, type 2 diabetes mellitus (DM), myocardial infarction, and stroke [5,10]. Although significant evidence connects PCOS to metabolic and cardiovascular risk, the underlying mechanisms remain complex and multifactorial, likely influenced by genetic, hormonal, and environmental factors [10,11]

This narrative review intends to prepare a comprehensive overview of the present evidence on cardiovascular risk in women with PCOS, examining how factors such as obesity, insulin resistance, and hyperandrogenism contribute to cardiovascular dysfunction in this population. By consolidating findings from epidemiological, clinical, and mechanical studies, this review seeks to improve understanding of the cardiovascular consequences of PCOS, highlight gaps in the current research, and discuss potential strategies for early intervention and risk reduction in affected women. This is particularly important given that early identification and management of cardiovascular risk factors could improve long-term health outcomes for women with PCOS, who are otherwise at increased risk for cardiovascular complications.

Overview

PCOS is one of the most frequent and complicated diseases of the endocrine system that affects the reproductive system of women in both developed and developing countries [13,14].

Micro polycystic ovaries, abnormality in Metabolism, menstrual disorders, and hyperandrogenism are characteristics of PCOS [15].

The prevalence of PCOS is 6%–10% in women of childbearing and is associated with acne, impaired glucose metabolism, diabetes, obesity, and insulin resistance (IR) although nonalcoholic fatty liver, cardiovascular

disease, and endometrial cancer are conditions with more probability appearance [15,16].

PCOS also indicated as a chronic inflammatory disorder that inflammatory factors play a prominent role in the pathogenesis through the higher expression of inflammatory cytokines as reported the serum elevation of IL-6, TNF-α and CRP in comparison to normal population [18, 19].

Dyslipidemia as one of the metabolic disorders associated with hirsutism causing reproductive difficulties in PCOS papulation, due to reduced levels of high-density lipoprotein cholesterol (HDL-C) and elevated levels of triglycerides. gut microbiota disorder is a metabolic condition which through the changes in critical sexual hormones can result in several disorders of ovarian function and metabolism [19-22].

It is indicated that prostaglandins, chemokines, cytokines and various pro-inflammatory mediators, have a significant role in autoimmune sexual diseases and PCOS. CXC-chemokine ligand 13 (CXCL13) is a chemoattractant of B lymphocyte that among with Chemokine receptor type 5 (CXCR5) as its receptor, are revealed in high levels in patients with inflammatory reproductive disorders and due to upgrade elevation in PCOS women ovaries, therapeutic processes against them may be done. But there is no adequate scientific research to report it and more ones are needed [23].

Acorrding to several researches and approaches of clinical science in the field of PCO, the relationship between IR and this metabolic disorder is clearly known, so that different abnormalities in insulin signaling specially in post-insulin receptor and the signaling pathway of phosphatidylinositol trikinase are effectively involved in the appearance of PCO [28, 29].

PCOS is a disease which due to endothelial damage, as a critical and major risk factor, can lead to various conditions with cardiovascular disease; for instance, a 10_fold increased stroke is an outcome of the disease along with systemic lupus erythematosus (SLE) and positive antinuclear antibody (ANA) [27].

The pathogenesis of PCOS is not clearly known; however genetic factors and lifestyle may have basic rules in the prevention of PCOS and CVD associated risk factors [28].

1.Overview of Cardiovascular Disease (CVD):

Cardiovascular diseases (CVD) encompass a range of disorders impacting the heart and blood vessels, including coronary artery disease, heart failure, arrhythmias, and myocardial infarctions. These conditions are predominantly precipitated by risk factors such as hypertension, diabetes, hyperlipidemia, and detrimental lifestyle choices [29]. CVD can result in severe complications, including compromised cardiac function and vascular damage, and ranks among the foremost causes of morbidity and mortality globally. Comprehending these diseases and their fundamental mechanisms is vital for effective prevention and treatment. Polycystic ovary syndrome (PCOS) is a significant risk factor for cardiovascular disease in women of reproductive years. Timely identification and suitable interventions are imperative to mitigate the risk of cardiovascular complications [30].

According to Zhang et al. [31], women with PCOS are at an elevated risk for CVD compared to non-PCOS women. The analysis of the data shows that these women have approximately 1.66 times higher likelihood of developing cardiovascular disease [31].

1.1. Acute Coronary Syndrome (ACS):

Acute coronary syndrome (ACS) refers to a collection of diseases resulting from an abrupt decrease in blood supply to the cardiac muscle (ischemia). The conditions encompass unstable angina, myocardial infarction (MI), and cardiac arrests [32]. ACS is generally initiated by the rupture of atherosclerotic plaques and the subsequent production of thrombi in the coronary arteries, impeding blood supply to the myocardium. This may lead to chest discomfort, diminished cardiac function, and in extreme instances, heart failure or mortality [32]. The transition from unstable to stable conditions may be gradual, occasionally encompassing arterial spasms or microvascular complications. Elevated testosterone levels and central adiposity facilitate plaque accumulation in coronary arteries, impeding blood flow to the cardiac muscle and heightening the risk of myocardial infarction [33].

1.2. Heart Failure (HF):

Heart failure (HF) is a multifaceted clinical condition arising from anatomical or functional deficiencies in ventricular filling or blood ejection. The primary symptoms consist of dyspnea, tiredness, and fluid accumulation, resulting in edema or pulmonary congestion. HF may result from abnormalities of the pericardium, myocardium, endocardium, heart valves, or major arteries, however it is predominantly linked to compromised left ventricular (LV) function. HF is categorized according to left ventricular ejection fraction (EF) into heart failure with reduced EF (HFrEF) and heart failure with preserved EF (HFpEF), each exhibiting unique features, risk factors, and therapeutic responses. HFrEF is predominantly observed in men and frequently associated with comorbidities such as diabetes and hypertension, while HFpEF is more prevalent in elderly women with a history of hypertension [34]. Insulin resistance and hypertension compel the heart to exert greater effort over time, resulting in the deterioration of the cardiac muscle and, ultimately, heart failure [29].

1.3. Hypertension:

Hypertension, defined by persistently high blood pressure, is a major risk factor for CVD and overall morbidity. While most cases are essential hypertension with no known cause, about 10% are secondary, linked to identifiable factors [36]. The pathophysiology involves complex interactions between genetic, environmental, and hormonal factors, affecting organs like the kidneys, cardiovascular system, and central nervous system. If untreated, hypertension can lead to organ damage and increased cardiovascular risk [36]. In women with PCOS, insulin resistance and chronic inflammation contribute to blood vessel constriction and fluid retention, raising blood pressure and adding strain to the heart [37].

1.4. Arrhythmia:

Arrhythmia is a term that describes any irregularity in the normal rhythm of the heart as it beats. PVCs, which are premature or irregular heartbeats, and ventricular tachycardia, which is an abnormal and rapid heart rhythm, are two examples of the symptoms that can be caused by these illnesses. These conditions can manifest themselves in a variety of ways, such as monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, or ventricular fibrillation (VF) [37]. Certain arrhythmias might result in major hazards, such as abrupt cardiac arrest or sudden cardiac death, which need rapid treatment and, in some cases, more complex medical procedures [37]. In PCOS, hormonal imbalance and high androgen levels can have an effect on the electrical conduction of the heart, which can lead to abnormal heart beats, often known as arrhythmias [38].

1.5. Thrombosis:

Thrombosis is a significant cardiovascular risk for women with PCOS, presenting as either venous thromboembolism (VTE) or arterial thrombosis. The increased thrombotic risk in PCOS is associated with hormonal imbalances, insulin resistance, obesity, and systemic inflammation, all of which contribute to a heightened propensity for blood clotting [39, 40].

1.5.1. Venous Thrombosis:

Women with PCOS, especially those on hormonal therapy (e.g., oral contraceptives), are at an elevated risk of VTE. Increased estrogen levels, frequently observed in women with PCOS, enhance coagulation activity, hence elevating the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE). Insulin resistance, commonly observed in PCOS, is also linked to heightened pro-thrombotic factors, hence amplifying the risk of thrombosis [39]. Women with PCOS face an elevated risk of venous thrombosis due to variables such as obesity, chronic inflammation, and hormone dysregulation. Increased testosterone levels and insulin resistance may alter blood flow and enhance clotting propensity, hence elevating the risk of diseases such as DVT [41].

1.5.2. Arterial Thrombosis:

Though less common, women with PCOS also run a danger from arterial thrombosis. Both common in PCOS, chronic inflammation and endothelial dysfunction help to produce atherosclerotic plaques, which raise artery clot formation risk. Events including myocardial infarction or stroke can follow from this. Insulin resistance aggravates these consequences and causes systemic vascular damage that increases women with PCOS' risk of cardiovascular events [40]. Particularly those with high androgen levels, women with PCOS run a higher risk of subclinical atherosclerosis, which is characterized by thickening of the carotid artery wall and plaque development in coronary arteries. The metabolic problems and insulin resistance linked to PCOS raise the risk of clot development and arterial thrombosis, which can cause heart attack and stroke. This link emphasizes PCOS as a thrombosis risk factor, fit for inclusion in the part on thrombosis in your paper [42].

1.6. Stroke

Stroke results from the interruption of blood flow to the brain, causing swift cellular damage. This disruption may result from narrowed or ruptured vessels (hemorrhagic stroke) or from a blockage caused by a clot (ischemic stroke). The four main categories of stroke include ischemic, hemorrhagic, transient ischemic attack (TIA), and cryptogenic stroke The ischemic type is the most prevalent and is consequently the subject of extensive research. Evidence regarding sex differences in hemorrhagic stroke remains contentious and may vary based on the affected brain region, whereas sex differences in other stroke types are negligible. Stroke ranks as the second leading cause of death worldwide and the fifth in the United States, with ischemic strokes constituting 71% of cases. Stroke incidence is higher in older men; however, the risk increases in women as they age and experience a decline in estrogen levels. Hypertension and atherosclerosis in PCOS may diminish cerebral blood flow and elevate the risk of vascular rupture, thereby increasing the likelihood of stroke [43].

2.Mechanisms Linking PCOS and Cardiovascular Risks:

2.1Metabolic Disorders in PCOS and Their Link to Cardiovascular Risks

PCOS is commonly linked to metabolic disorders that elevate the risk of cardiovascular diseases among affected individuals. Obesity, commonly observed in individuals with PCOS, significantly contributes to the worsening of these metabolic disorders by inducing insulin resistance and increasing insulin levels [44].

2.1.1. Obesity

Obesity is linked to elevated insulin levels and insulin resistance, a condition that may heighten the risk of type 2 diabetes, hypertension, and dyslipidemia [45]. Meteorin-like protein (Metrnl), an adipokine, is implicated in the regulation of energy balance and inflammatory processes. Research indicates that women with PCOS, especially those experiencing obesity and recurrent pregnancy loss (RPL), exhibit reduced levels of this protein. Lowered Metrnl levels correlate with diminished insulin sensitivity and disrupted glucose homeostasis, both of which are associated with an increased risk of cardiovascular issues. In women with obesity and PCOS, especially those experiencing infertility, reduced levels of Metrnl may signify heightened metabolic dysfunction and an elevated risk of cardiovascular disease [46].

2.1.2. Insulin Resistance:

PCOS is characterized by insulin resistance, which primarily arises from a defect in insulin signaling. This condition is associated with a decrease in GLUT4 expression and a reduction in the β-subunit of the insulin receptor within visceral adipose tissue, resulting in impaired glucose uptake in adipocytes [47]. Furthermore, the adrenal glands and ovaries exhibit sensitivity to insulin, resulting in steroid synthesis, whereas tissues such as adipose tissue, skeletal muscle, and the liver demonstrate increased resistance to the metabolic effects of insulin. This leads to insulin resistance that is specific to certain tissues, while steroid-producing tissues continue to respond to insulin [47].

Insulin resistance is frequently observed in individuals with PCOS; however, it is important to note that not every woman diagnosed with PCOS exhibits insulin resistance. Insulin resistance in PCOS has been identified in adipocytes as a post-binding defect in the insulin receptor-mediated signal transduction. This phenomenon has also been validated through clinical studies focusing on skeletal muscle action [48]. Furthermore, research involving skin fibroblasts has indicated that impairments in insulin signaling result from diminished activity of insulin receptor tyrosine kinase. The observed impairment is linked to heightened serine phosphorylation of receptors, which is influenced by a serine kinase that is external to the receptor itself. This process results in a specific resistance to the metabolic effects of insulin [48].

Various additional factors may play a role in the development of insulin resistance and hyperinsulinemia, including the rise in testosterone levels that occurs during puberty. Research has explored the relationship between hypoandrogenic states and insulin resistance, highlighting a correlation with uncommon autoimmune disorders that impact insulin receptors and exhibit hypo androgen characteristics [47].

Insulin resistance in PCOS is linked to an elevated ED50 for glucose uptake in response to insulin, signifying resistance [43]. Furthermore, the buildup of ceramides and diacylglycerol (DAG) within the liver and muscle tissues disrupts insulin signaling pathways. Intracellular ceramides exert a detrimental influence on insulin signaling by inhibiting the translocation of protein kinase B (Akt), which is a crucial modulator of insulin sensitivity, to the plasma membrane [47].

Insulin resistance contributes to metabolic disorders, including glucose intolerance and dyslipidemia, while also heightening the risk of cardiovascular disease due to chronic inflammation [45]. Dysregulated insulin signaling in the central nervous system has been associated with obesity and impaired ovarian follicular maturation, indicating additional relationships among obesity, PCOS, and hyperinsulinemia [47].

2.1.3. Metabolic Syndrome in Women with PCOS

Studies show that metabolic syndrome (MetS) is notably prevalent among women with PCOS, occurring at a rate of approximately 29.5%, which is significantly higher compared to the general population, where the prevalence is around 4.8% in healthy women. Abdominal obesity, elevated blood glucose levels, high blood pressure, and low HDL cholesterol are significant risk factors for Metabolic Syndrome. Each of these factors plays a role in heightening the risk of cardiovascular disease. Furthermore, research indicates that women diagnosed with PCOS often encounter insulin resistance, hyperandrogenism, and chronic inflammation, factors that may contribute to an increased risk of cardiovascular issues [49].

2.1.4. Chronic Inflammation and Reactive Oxygen Species (ROS):

In individuals with PCOS, the presence of obesity and insulin resistance contributes to elevated levels of reactive oxygen species (ROS) and pro-inflammatory cytokines. The inflammatory responses observed, especially in individuals with visceral obesity, may worsen insulin resistance and elevate the risk of diabetes and metabolic disorders. Chronic inflammation is acknowledged as a significant mechanism contributing to cardiovascular risks in individuals with PCOS [45]. Individuals diagnosed with PCOS exhibit elevated levels of chronic inflammatory markers, including CRP, TNF-α, endothelin-1, and homocysteine [43].

2.1.5. Genetic Factors and β-cell Dysfunction:

PCOS has a strong genetic component, with approximately 70% concordance in twins. Family studies have shown that both male and female first-degree relatives of women with PCOS exhibit reproductive and metabolic abnormalities, such as insulin resistance and β-cell dysfunction. Environmental factors such as diet and physical activity levels also interact with these genetic predispositions, further exacerbating insulin resistance and metabolic dysfunction in women with PCOS. Early β-cell dysfunction has been observed in adolescent girls whose mothers have PCOS, indicating that these metabolic disturbances can appear even before puberty [50].

2.2. Hormonal Disorders:

In PCOS, hormonal imbalances play a crucial role, affecting both ovulation and androgen levels. The dysregulation of gonadotropins influences the release of LH and FSH [47], which plays a role in hyperandrogenism and complications related to ovulation [48]. Increased levels of androgens, resulting from elevated luteinizing hormone (LH), are associated with heightened cardiovascular risks. The decline in estrogen production, frequently associated with diminished aromatase activity, has significant implications for reproductive health and may elevate cardiovascular risks, including the potential for stroke [43].

2.2.1. Gonadotropin Dysregulation

In PCOS, gonadotropins LH and FSH, which regulate ovulation and ovarian steroid production, are released abnormally, although these changes are not diagnostic. Since hyperandrogenism and ovulatory dysfunction are key features of PCOS, altered gonadotropin secretion may influence these characteristics. Increased LH pulse frequency, higher LH/FSH ratios, elevated LH levels, and low FSH levels are common in women with PCOS [47]. However, some obese women with PCOS may have normal LH levels, highlighting the diversity of the syndrome. The separation of GnRH and LH release may explain why some women with PCOS, especially those with obesity, secrete less LH despite the role of LH as a marker of GnRH pulses [47].

In the context of PCOS, the gonadotropins LH and FSH, which play a crucial role in regulating ovulation and the production of ovarian steroids, are released in an abnormal manner; however, these alterations are not definitive for diagnosis. Hyperandrogenism and ovulatory dysfunction are fundamental aspects of PCOS, suggesting that changes in gonadotropin secretion could impact these traits. Women with PCOS often exhibit increased LH pulse frequency, elevated LH/FSH ratios, heightened LH levels, and reduced FSH levels [47]. Nonetheless, certain obese women diagnosed with PCOS may exhibit normal LH levels, underscoring the heterogeneity of the syndrome. The distinction between GnRH and LH release may elucidate the phenomenon observed in certain women with PCOS, particularly those who are obese, who exhibit reduced LH secretion despite LH serving as an indicator of GnRH pulses [47].

2.2.2Hyperandrogenism:

In PCOS, there is an elevation in the secretion of gonadotropin-releasing hormone (GnRH), which occurs in an irregular pattern, resulting in an increase in luteinizing hormone (LH) production. The increased levels of LH enhance the function of theca cells within the ovaries, leading to an augmented synthesis of testosterone and various other androgens. The inadequate levels of follicle-stimulating hormone (FSH), essential for the activation of granulosa cells, hinder the complete conversion of testosterone to estrogen [48]. As a result, there is an increase in testosterone levels, while estradiol and progesterone lose their regulatory influence over the hypothalamic-pituitary axis, leading to diminished negative feedback and the continuation of excessive androgen production [48].

While androgen excess is frequently regarded as a defining characteristic of PCOS, it is estimated that merely 80-85% of women exhibiting clinical hyperandrogenism receive a diagnosis of this condition [51].

Research conducted by the Women's Ischemia Evaluation Study (WISE) indicates that postmenopausal women diagnosed with PCOS and exhibiting elevated levels of free testosterone face a heightened risk of cardiovascular events. In this research, 32% of women diagnosed with PCOS exhibited multi-vessel cardiovascular disease, in contrast to 25% observed in the control group. The results indicate a clear association between hyperandrogenism and an increased risk of cardiovascular disease, especially among postmenopausal women diagnosed with PCOS [52].

Furthermore, in individuals diagnosed with PCOS, insulin and visceral fat contribute to the increased production of adrenal androgens. This condition is linked to an increase in fat accumulation in particular regions of the body, while the liver's synthesis of sex hormone-binding globulin (SHBG) diminishes, resulting in elevated concentrations of free testosterone in the bloodstream [53].

The relationship between androgens and increased blood pressure in women with PCOS had not been previously determined. In a recent publication of Hypertension, Chen and colleagues investigated the impact of androgens on hypertension among young women diagnosed with PCOS. The research conducted on a group of Taiwanese women, averaging 24 years of age, demonstrated a significant association between both the free androgen index and total testosterone levels with systolic and diastolic blood pressure [36]. The results suggest that androgens could play a role in elevating blood pressure among women with PCOS, although the exact mechanisms responsible for this phenomenon have yet to be completely elucidated [36].

Increased levels of testosterone are associated with a heightened risk of stroke. This phenomenon can be attributed to elevated levels of free testosterone, which are more efficiently converted into active forms. The relationship between testosterone and stroke remains a topic of ongoing discussion; however, research indicates that increased levels of testosterone may affect stroke risk by influencing cardiovascular health. Furthermore, other androgens such as DHEA and DHT, which are also elevated in PCOS, may contribute to an increased risk of stroke by affecting cardiovascular function [43]

2.2.3Estrogen Imbalance and Its Implications:

In women experiencing hormonal disorders such as PCOS, the regulation of estrogen may be disrupted, even when hormone levels appear to be within the normal range in certain instances. This phenomenon frequently arises from extra-gonadal aromatization, in which adipose tissue transforms androgens into estrogen [43]. Nonetheless, the conversion process exhibits limitations in its effectiveness, especially when elevated androgen levels are present, leading to potential disruptions in the normal feedback functions of estrogen [43].

Reduced aromatase activity in the ovaries, essential for the conversion of androgens to estrogen, results in diminished availability of estrogen. This disruption may impact reproductive health by leading to menstrual irregularities, anovulation, and infertility [43]. Furthermore, the dysregulation of other hormones such as LH and androgens may additionally affect the regulation of estrogen, thereby complicating the

hormonal profile observed in these disorders. In women diagnosed with PCOS, the disruption of estrogen production and the impaired conversion of androgens into estrogen result in the loss of this protective effect. This condition can result in a heightened risk of cardiovascular diseases and stroke [43].

2.3. Cholesterol and Lipid Abnormalities:

Dyslipidemia represents a prevalent metabolic disorder in women diagnosed with PCOS, frequently associated with insulin resistance, resulting in diverse abnormalities in lipid profiles. These encompass decreases in HDL cholesterol alongside increases in triglycerides and LDL cholesterol levels. Alongside these quantitative changes, qualitative modifications are also observed in patients with PCOS. It is important to highlight that there exists a greater prevalence of small, dense LDL particles, which possess a higher atherogenic potential compared to the larger, buoyant particles generally observed in healthy individuals [54].

Women diagnosed with PCOS often exhibit low levels of HDL cholesterol, which plays a significant role in diminishing reverse cholesterol transport. This process is essential for the removal of excess cholesterol from peripheral tissues and its subsequent transport back to the liver for elimination. The modification in lipid metabolism represents a significant contributor to the increased cardiovascular risk observed in individuals with PCOS [54].

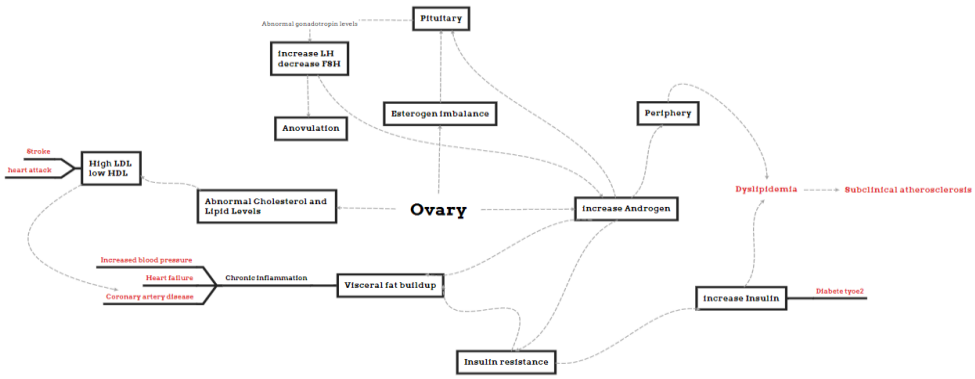

Figure 1

This mind map illustrates the complex interactions between metabolic and hormonal disorders in Polycystic Ovary Syndrome (PCOS) and their impact on cardiovascular health. Key factors, including insulin resistance, hyperandrogenism, cholesterol abnormalities, and central obesity, contribute to an increased risk of cardiovascular diseases through pathways such as chronic inflammation, atherosclerosis, and hypertension. The imbalance of LH and FSH in PCOS also leads to elevated androgen production and ovulatory dysfunction, which further influences cardiovascular and metabolic health. This visualization helps readers understand the interconnected pathways by which PCOS impacts cardiovascular risk.

2.4 Cardiovascular and Pregnancy-Related Risks

Women who experience specific hormonal imbalances face an increased likelihood of encountering complications during pregnancy. These complications may include preeclampsia, eclampsia, peripartum cardiomyopathy, heart failure, acute kidney injury, and pulmonary edema. The presence of these complications leads to a heightened cardiovascular burden both during and following pregnancy, thereby requiring more intensive hospital care. The average duration of hospital stays and the related expenses are markedly elevated in these instances, underscoring the necessity for comprehensive monitoring and management [55].

Comorbidities and risk factors

Women with PCOS are frequently linked to a higher incidence of CVD risk factors [56]. Given the considerable diversity among women with PCOS, CVD risk profiles can vary based on the specific PCOS phenotype [57].

Those with PCOS who experience obesity, dyslipidemia, hypertension, and impaired glucose tolerance (IGT) are at an increased risk, while individuals with metabolic syndrome and/or type 2 diabetes mellitus face a heightened risk for CVD [58].

In addition to the metabolic and CVD risk factors previously discussed, other factors such as sleep disturbances and mood disorders also contribute to the health challenges faced by women with PCOS [58, 59]. Hence, early prevention and management of potential cardiovascular complications are essential [56].

In the following, we will examine these risk factors in detail.

PCOS phenotypes

A critical factor in assessing CVD risk in women with PCOS is how the condition is defined. Countless efforts were made to categorize PCOS [58]. Ultimately, in 2012, the National Institute of Health (NIH) consensus panel defined four distinct PCOS phenotypes (A, B, C, and D) [60]. Phenotypes A and B were labeled as "classic PCOS." Phenotype A included patients with hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology, while phenotype B was characterized by hyperandrogenism and ovulatory dysfunction. Phenotype C was referred to as "ovulatory PCOS" and encompassed patients with hyperandrogenism and polycystic ovaries. Finally, phenotype D, referred to as non-hyperandrogenic PCOS, included those with polycystic ovaries and ovulatory dysfunction [61]. PCOS is particularly regarded as a significant risk factor for CVD, especially in patients with Phenotypes A and B, where hyperandrogenism, abdominal obesity, and insulin resistance (IR) are more pronounced [62]. Individuals with ovulatory PCOS typically exhibit a lower body mass index (BMI) and reduced abdominal fat, alongside milder symptoms of hyperandrogenism, hyperinsulinemia, and less severe dyslipidemia [58]. In comparison, patients with non-hyperandrogenic PCOS typically show the most favorable metabolic profile, often similar to that of women without the condition [58].

IR

IR is a key factor in the development of PCOS and acts as a strong indicator of cardiometabolic risks [63]. IR in PCOS results from a reduced tissue sensitivity to insulin, often due to structural abnormalities in insulin receptors, impaired signaling pathways, or, in some cases, high levels of insulin-binding antibodies [64]. Hyperinsulinemia, which results from IR, promotes androgen production in the ovaries by activating theca cells [65]. Theca cells respond to elevated insulin levels by producing excess androgens, which disrupt the normal process of follicular maturation. This disruption leads to the development of polycystic ovarian morphology, a hallmark characteristic of PCOS [66].IR not only plays a key role in the development of PCOS but also negatively impacts long-term health by increasing the risk of serious conditions like Type 2 diabetes (T2DM) and CVD in affected patients [63].Studies indicate that a large percentage (50–80%) of people with PCOS are at an elevated risk for developing IR. Additionally, research suggests that conditions such as IGT and T2DM occur more frequently in individuals with PCOS than in non-PCOS controls, even when factors like age and weight are matched [67, 68]. Recent findings have associated IGT with a heightened risk of CVD, increased mortality, and T2DM in the general population [69]. Consequently, people with PCOS are exposed to a range of additional risks due to IR, including early adrenarche, elevated androgen levels, hirsutism, menstrual irregularities, central obesity, dyslipidemia, IGT, T2DM, endothelial dysfunction, hypertension, and an increased likelihood of early CVD. This underscores the urgent need for early diagnosis and effective management of IR in patients with PCOS [67].

Obesity, Especially Abdominal Obesity

More than half of women with PCOS are classified as overweight or obese, with a notable tendency toward central fat accumulation [70]. Obesity is a co-occurring risk factor in individuals with PCOS. Research indicates that IR is a primary driver of obesity in this population, as it leads to hyperinsulinemia. Elevated insulin levels stimulate steroid production in both the ovaries and adipose tissue, which lowers the liver's release of sex hormone-binding globulin (SHBG). This reduction causes an increase in free androgens. Over time, chronically elevated androgen levels contribute to central obesity by promoting visceral fat accumulation. This, in turn, worsens PCOS symptoms and creates a continuous cycle of metabolic and hormonal imbalances [71,72] Given that IR is a primary factor contributing to obesity in PCOS, the presence of central obesity further exacerbates insulin-related metabolic issues. These include hyperandrogenemia, menstrual irregularities, dyslipidemia, HTN, and an increased risk of T2DM [60]. These compounded metabolic disturbances make women with PCOS more susceptible to CVD, further amplifying their health risks [60]. Losing weight can offer significant benefits to obese women with PCOS. It can lead to reduced body fat, lower androgen and insulin levels, improved ovulatory function, enhanced fertility, and a decreased overall risk of CVD. These positive outcomes highlight the importance of weight management in reducing the complications associated with PCOS [73, 75].

Dyslipidemia

Dyslipidemia is characterized by abnormal lipid profiles, such as having Low-density lipoprotein (LDL) cholesterol levels exceeding 160 mg/dL, High-density lipoprotein

(HDL) cholesterol levels below 40 mg/dL, triglycerides (TG) above 200 mg/dL, or the use of cholesterol-lowering medications [76] These lipid abnormalities are strongly linked to IR and are known to be predictors of CVD, including myocardial infarction (MI) [5].The combined effects of obesity, IR, and elevated androgen levels are believed to contribute to dyslipidemia in women with PCOS [5]. Mechanisms include IR, increased production of very-low-density lipoprotein (VLDL), disrupted lipolysis due to impaired lipoprotein lipase function, and insulin signaling pathway dysfunction caused by the overexpression of the PI3KR1 gene [77]. These disruptions lead to excess fat accumulation, further connecting dyslipidemia to PCOS. Additionally, IR can lead to increased hepatic production of apoB-containing VLDL, causing hypertriglyceridemia [76]. Elevated testosterone levels in PCOS patients also contribute to dyslipidemia by causing androgen receptor-mediated IR and upregulating genes that accelerate HDL cholesterol breakdown, which is the "good" cholesterol [77]. Consequently, the prevalence of dyslipidemia is higher in women with PCOS [66]. Research has shown that PCOS patients have elevated LDL and non-HDL cholesterol levels, regardless of their BMI, along with characteristic changes in TG and HDL cholesterol [60]. Therefore, it is essential to screen all women with PCOS for dyslipidemia, including LDL and non-HDL cholesterol levels, to manage and prevent cardiovascular risks effectively [60].

Hypertension

The American College of Cardiology (ACC) and the American Heart Association (AHA) categorize hypertension as having a systolic blood pressure (SBP) of at least 130 mmHg or a diastolic blood pressure (DBP) of 80 mmHg or more. Using these benchmarks, research has revealed that women with PCOS have a 24% higher prevalence of hypertension compared to women without the syndrome [78]. One factor contributing to hypertension in PCOS patients is the activation of the renin-angiotensin system [79]. Evidence indicates that women with PCOS have higher levels of aldosterone than those matched for age and BMI, suggesting a hormonal pathway that could elevate their risk of developing hypertension [79]. Additionally, other mechanisms such as imbalances in the autonomic nervous system, enhanced renal sodium reabsorption, and diminished nitric oxide production has been linked to the onset of hypertension in women with PCOS [78]. These factors work together, affecting vascular and kidney functions and contributing to the higher incidence of hypertension in this group [78]. Women with PCOS and hypertension often exhibit signs of endothelial dysfunction, including reduced flow-mediated dilation of the brachial arteries, greater intima-media thickness (IMT) of the carotid artery, and increased serum endothelin-1 levels [80]. These markers suggest early vascular damage, including structural and biochemical changes predisposing them to atherosclerosis and other cardiovascular complications [80]. Consequently, hypertension in women with PCOS raises the risk of severe cardiovascular outcomes, such as atherosclerosis and MI. This increased risk not only affects individual health but also contributes to higher morbidity and mortality rates, thereby impacting the overall prevalence of CVD in the community [60].

Metabolic Syndrome

Metabolic Syndrome is characterized by a set of criteria that include high fasting blood glucose (≥5.6 mmol/L), low levels of high-density lipoprotein (HDL) cholesterol (<1.29 mmol/L), elevated triglycerides (TG) (≥1.7 mmol/L), central obesity (defined by waist circumference adjusted to regional and population-specific standards), and increased blood pressure (systolic or diastolic ≥130/80 mmHg) [81]. Metabolic Syndrome is significantly more common in women with PCOS, with an estimated prevalence of 40–50%, compared to lower rates seen in the general population [82]. The occurrence of Metabolic Syndrome in individuals with PCOS is largely attributed to IR. Each clinical component of metabolic syndrome is associated with distinct underlying mechanisms. For instance, hypertension is linked to endothelial damage and decreased bioavailability of nitric oxide, while dyslipidemia is influenced by IR through the elevated release of non-esterified fatty acids and increased TG production. Additionally, IR contributes to hyperglycemia through compensatory hyperinsulinemia and the eventual depletion of pancreatic beta cells [83, 84]. Metabolic Syndrome represents a combination of multiple metabolic elements that are already recognized as established risk factors for CVD. These include IGT, IR, T2DM, dyslipidemia, obesity, and hypertension [85]. Even teenagers with PCOS frequently exhibit IGT, T2DM, and Metabolic Syndrome [86]. This indicates that PCOS adversely affects metabolic health throughout a

woman's life, further adding to the societal burden of chronic diseases like T2DM, hypertension, and cardiovascular CVD [86].

Sleep disturbances

Women with PCOS seem to experience sleep problems more frequently than the general population [88, 89]. Sleep issues, including difficulty initiating sleep, waking up early, and inconsistent sleep duration, can severely impact cardiovascular health. These disturbances are associated with an increased risk of stroke, coronary artery disease, and hypertension

[89,90]. Recent studies have shown that unhealthy sleep patterns are linked to the development of metabolic disorders in adolescents with PCOS [89]. Prolonged poor sleep habits can impair metabolic function, leading to a higher risk of developing metabolic syndrome in individuals with PCOS [59]. In women with PCOS, sleep disturbances have been associated with increased BMI, SBP, DBP, and LDL cholesterol levels, as well as decreased HDL cholesterol [59]. Women with PCOS who experience sleep disturbances show elevated levels of fasting plasma glucose and 2-hour glucose, both recognized as cardiovascular risk factors. Disruptions in sleep structure may lead to changes in glucose metabolism, affecting overall health [91].

In short, sleep issues in women with PCOS are associated with an increased cardiovascular risk profile, making it crucial to screen for CVD in women with PCOS [59].

Depression, anxiety, and reduced quality of life

Depression and mood disorders are not only significant risk factors for CVD but are also highly common in women with PCOS [58]. This connection underscores the complex relationship between mental health and cardiovascular risk in this group [53].

Research increasingly shows that women with PCOS are more likely to experience depression and anxiety. These conditions are often worsened by dissatisfaction with body image, which can negatively affect overall well-being. Such emotional struggles may lead to symptoms like fatigue, sleep disturbances, changes in appetite, and binge eating episodes, which further complicate their mental and physical health [92,94].

Women with PCOS who are also dealing with depression tend to have a BMI and IR, both of which heighten cardiovascular risk [93]. This occurs even though their levels of androgen excess are comparable to those of non-depressed women with PCOS [93]. Weight loss through a calorie-restricted diet has been found to positively impact mood, reduce symptoms of depression, and improve the quality of life in women with PCOS [95].

Future directions and research gaps

This article focuses on cardio-metabolic aspects only in the light of PCOS, ignoring other independent risk factors like smoking, menopause, stress, family history, and the multi-factorial causation of PCOS with genetic and environmental influences have also not been explored.

Conclusion

In this research we explored cardiovascular risks in women with PCOS with emphasize on linking mechanisms, risk factors and comorbidities, besides giving an overview of PCOS and CVD. The gathered information demonstrated increased risk of CVDs such as HTN, ACS, HF, Arrythmias, stroke and thrombosis due to obesity, insulin resistance, metabolic, hormonal and lipid dysregulations along with inflammatory processes associated with PCOS. Genetic aspects in interaction with environmental factors may aggravate IR and β-cell dysfunction.[31,36,38,39,43,44,50] Another considerable factor in assessing CVD risk in these patients is the phenotype of PCOS based on classification of PCOS defined by NIH[57,58,60,61,62].Other associated issues, such as sleep disturbances and mood disorders are also significant risk factors for CVD.[58,59,93] These findings emphasize the importance of early detection and management of PCOS in order to prevent further complications specially adverse cardiovascular events. This matter requires incorporation of risk evaluation in PCOS patients into routine assessment and advancing general population's knowledge for in-time referral to medical centers and treatment adherence. B

Conflict Of Interest: The authors declare no conflicts of interest.

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DOI:10.31579/2690-1919/542