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REVIEW

Endothelial Dysfunction in Women and its Relationship with Infertility

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ABSTRACT

Endothelial dysfunction is an early indicator in the development of atherosclerosis and cardiovascular diseases (CVD), and its evaluation in clinical settings is of great importance. Men are particularly at higher risk compared to premenopausal women, and the earlier onset of CVDs in men is associated with differences in estrogen levels between genders. Estrogen and testosterone regulate endothelial function through both genomic and non-genomic pathways, affecting vasodilation, inflammation, and cell proliferation. In women, polycystic ovary syndrome (PCOS) and endometriosis are associated with endothelial dysfunction. Although the relationship between endothelial dysfunction and female sex hormones has been demonstrated, its direct impact on female fertility remains unclear. Despite the connection between endothelial health and reproductive parameters, definitive markers for fertility and infertility have yet to be identified, making their use in clinical practice challenging. The polygenic nature of reproductive health further complicates the detection of specific markers. Therefore, despite significant advancements, further research is needed to identify reliable endothelial markers for fertility and infertility. This review focuses on the significance of the gender differences in endothelial dysfunction concerning cardiovascular diseases and fertility.

Keywords: Endothelial dysfunction, infertility, PCOS

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INTRODUCTION

Endothelial Dysfunction (ED) can lead to significant health consequences, including the onset and progression of Cardiovascular Diseases (CVDs). Beyond its cardiovascular implications, ED has emerged as a potential factor influencing reproductive health, particularly in women. Hormonal fluctuations, particularly involving estradiol and testosterone, significantly impact endothelial function. Estradiol, for instance, enhances Nitric Oxide (NO) production, reduces inflammation, and supports endothelial repair, providing cardiovascular protection in premenopausal women. However, its decline during menopause corresponds with an increased risk of CVD.

Similarly, conditions like Polycystic Ovary Syndrome (PCOS) and endometriosis, which are associated with hormonal and metabolic imbalances, frequently exhibit early signs of ED, contributing to both cardiovascular risks and fertility challenges. While the link between ED and cardiovascular health is well established, its effects on female fertility remain less understood. Emerging evidence suggests that ED may play a role in infertility, with conditions like PCOS and endometriosis offering unique insights into this relationship. Despite advancements, significant gaps persist in understanding how endothelial health impacts reproductive outcomes and identifying reliable biomarkers for fertility assessment. Exploring these interconnections is critical for improving both cardiovascular and reproductive health outcomes.

What is Endothelial Dysfunction?

The endothelium is a thin layer of cells, known as endothelial cells, that lines all the blood vessels and lymphatic vessels. The endothelium is crucial for keeping tissues in balance by producing various molecules that help with functions such as widening and narrowing blood vessels, controlling blood

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clotting, regulating immune responses, inflammation, and new blood vessel growth.[1] It also manages clot breakdown and balances oxidants and antioxidants. The vascular endothelium has several key roles:

1. Maintaining the integrity of blood vessel barriers;
2. Controlling vascular tone;
3. Regulation of hemostasis;
4. Preservation of anti-inflammatory, antioxidant, and anti-coagulant actions;
5. Regulation of anti-proliferative properties;
6. Regulation of cellular metabolism of adenosine triphosphate (ATP), glucose, and amino acids.

Additionally, NO plays a vital role in maintaining the health and function of the endothelium.[2]

Endothelial dysfunction is an early sign of atherosclerosis and the start of cardiovascular disease. ED is caused by increased oxidative stress, reduced NO production, and elevated secretion of specific factors that stimulate inflammatory pathways and cell proliferation. Evaluating endothelial health is essential in medical practice, and several direct and indirect indicators have been suggested to identify imbalances in endothelial function.[3]

Endothelial Dysfunction, Cardiovascular Disease, and Gender

Men are at a higher risk of developing cardiovascular diseases and tend to face these problems earlier than premenopausal women. This difference is mainly due to varying levels of estrogen. Estradiol levels and how its receptors work can differ between men and women, which helps explain why cardiovascular disease risks and timing can vary by gender.[1,4]

Although the genetic makeup of endothelial cells remains consistent throughout the body, their phenotypic expressions can vary significantly (Fig. 1). Recent advances, especially single-cell RNA sequencing (scRNA-seq), have revealed the unique transcriptomes of endothelial cells, both across different organs and within the vasculature of a single organ. For instance, endothelial cells exhibit zonation, which aligns with different vessel types, such as arteries, arterioles, and capillaries.

Sex hormones are essential in regulating vascular function and health. Estrogens, androgens, and progestogens

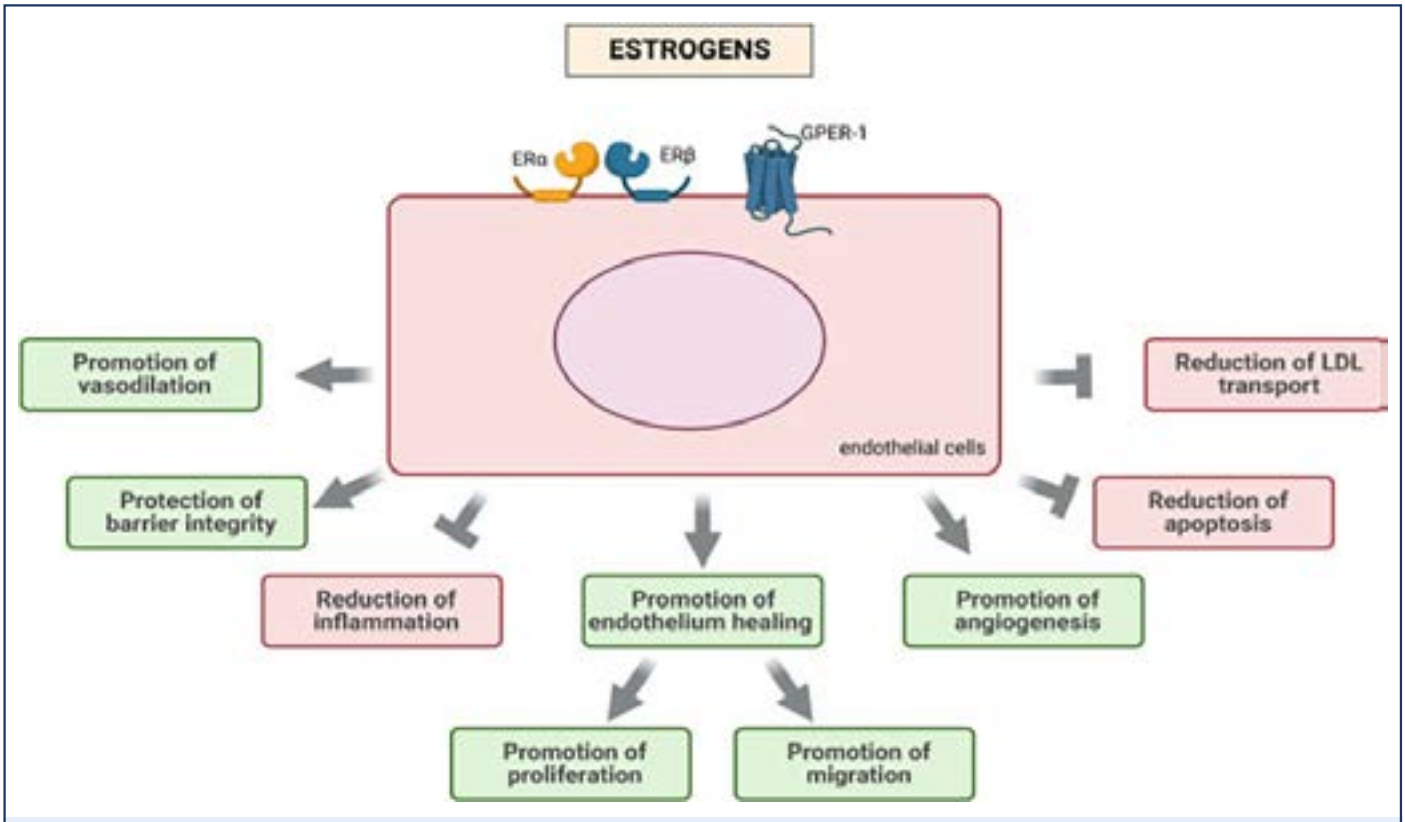

Figure 1. Estrogens and endothelial cell function[5]

LDL: Low-density lipoprotein

notably influence the health and function of endothelial cells. When these hormones bind to their specific receptors, estrogen can prompt two types of responses in the body. They can cause a quick reaction through signaling kinase pathways or a longer-lasting response by affecting gene transcription. Estrogens help endothelial-dependent vasodilation, angiogenesis, and endothelial repair by promoting cell growth and movement. They also reduce endothelial inflammation, cell death, and the movement of low-density lipoprotein (LDL) through the endothelium, ultimately helping maintain the stability of the endothelial barrier.[6–8]

Recent studies with mouse models show that estradiol demonstrates several vasoactive properties, extending beyond its physiological influence on reproductive function. According to the findings of these studies, estrogen likely plays a crucial role in regulating the endothelial functions that are vital for female reproductive health.[8] During the woman's fertile window, estradiol levels fluctuate cyclically, providing notable cardiovascular benefits. The hormone contributes to lowering total and LDL cholesterol levels and inhibits LDL oxidation, which is critical for preventing atherosclerosis. Additionally, estradiol helps reduce fibrosis and promotes angiogenesis and vasodilation, enhancing overall blood flow. It also supports mitochondrial function, essential for cellular energy production and health.[8,9]

A key mechanism by which estradiol exerts these effects is through the activation of endothelial nitric oxide synthase (eNOS). This enzyme catalyzes the production of nitric oxide (NO), a potent vasodilator. Estradiol's influence on eNOS transcription and NO production plays a crucial role in maintaining vascular health and facilitating flow-mediated dilation (FMD), a measure of endothelial function.

As women go through menopause, the levels of estradiol significantly decrease. This reduction contributes to an increased risk of cardiovascular disease (CVD), which approaches levels observed in men. Unlike during the fertile years, menopause does not affect the smooth vascular muscle's functionality but does reduce the hormonal regulation of endothelial cells. This diminished regulation leads to a higher susceptibility to cardiovascular issues due to the loss of estradiol's protective effects. The decline in estradiol levels during menopause highlights a critical shift, leading to an increased risk of cardiovascular conditions. Understanding these dynamics is essential for developing strategies to manage cardiovascular health across a woman's lifespan.

Estrogen affects the endothelium through three mechanisms:

1. Stimulating the production of vasodilator factors such as NO and prostacyclin,
2. Supporting the repair mechanisms for endothelial damage,
3. Displaying anti-inflammatory and antioxidant effects.

These effects are mediated through both genomic and non-genomic pathways. Genomic actions involve long-term changes in gene expression through estrogen receptors, while non-genomic actions lead to immediate effects through signaling pathways.[9,10]

While estrogen's effects have been extensively studied, the influence of testosterone on endothelial function is receiving more attention. Studies reveal that testosterone contributes to vasodilation through both genomic and non-genomic mechanisms.

When comparing males and females, the first myocardial infarction occurs approximately nine years earlier in males, on average. Although these molecular pathways are still being explored, testosterone influences cardiovascular health, cognitive function, and metabolic processes. Testosterone affects endothelial cells through two main mechanisms:

1. Genomic Mechanism: Testosterone increases the production of nitric oxide (NO) by binding to androgen receptors inside the cell nucleus. This process activates endothelial nitric oxide synthase (eNOS), which helps relax blood vessels.

2. Non-Genomic Mechanism: Testosterone also works through various membrane receptors, including the PI3K/AKT pathway, which also activates eNOS.

While the exact details of how testosterone impacts endothelial cells are still being studied, it's clear from studies that testosterone directly affects blood vessel function. Unlike estrogen, which is synthesized from testosterone in the body, testosterone's effects are not mediated through these estrogens. For testosterone to effectively cause blood vessel dilation, the endothelium (the inner lining of blood vessels) must function properly.[9] In cases where the endothelium is damaged or not working well, higher testosterone levels are required to achieve the same effect. Additionally, dihydrotestosterone (DHT), a form of testosterone that does not convert into estrogen, also helps in dilating blood vessels.

The differences in how testosterone and estradiol affect blood vessel function may help explain why men and women experience cardiovascular events differently. For example, men typically have their first heart attack about nine years earli-

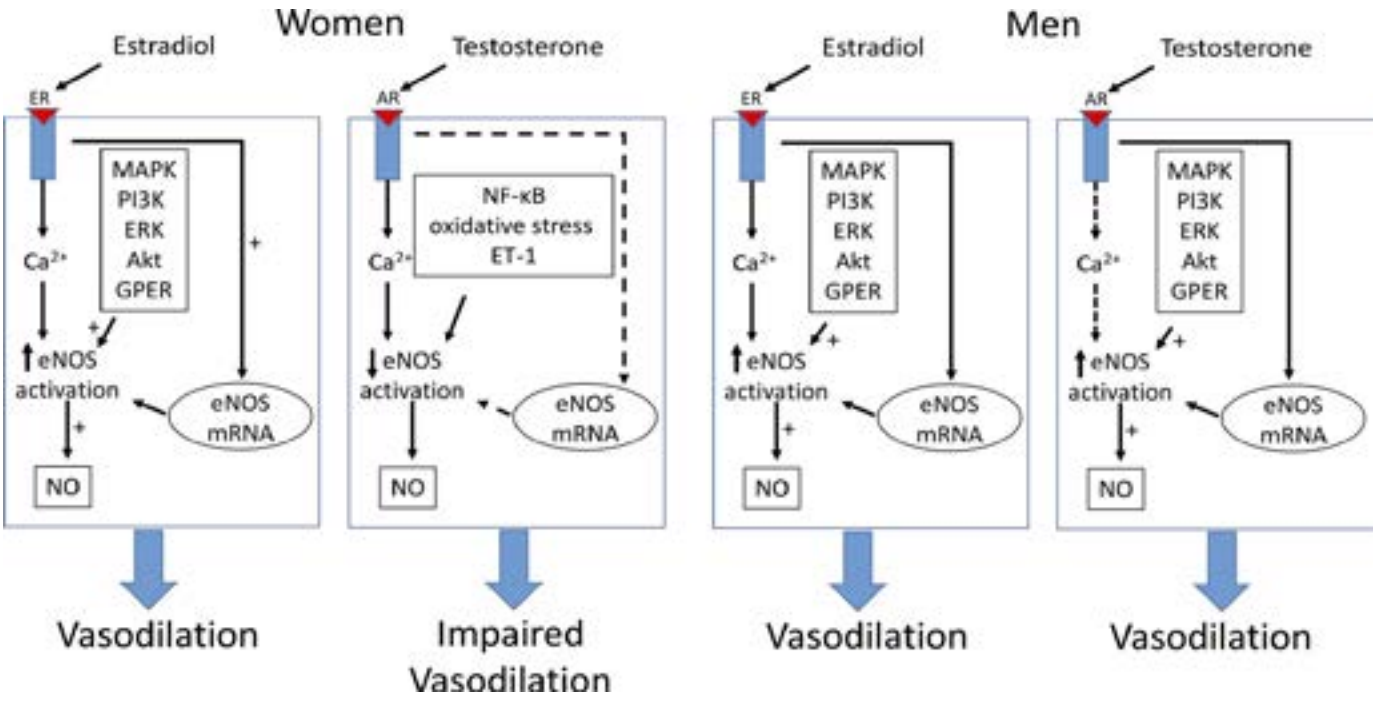

Figure 2. Sex differences in eNOS activation by estradiol and testosterone impact vascular response

eNOS: Endothelial nitric oxide synthase

er than women. Both estradiol and testosterone play crucial roles in regulating endothelial function, but they do so in different ways and at different concentrations. These hormonal effects and other factors like microRNAs contribute to the differences in cardiovascular health between genders.[10,11]

Estradiol increases NO availability in men and women, while testosterone has similar effects in men but reduces NO availability and impairs vasodilation in women. The dashed line indicates uncertain effects. ER, estrogen receptor; AR, androgen receptor; PI3K, phosphoinositide 3-kinase; GPER, G protein-coupled estrogen receptor 1.[12]

This evidence highlights the differences in endothelial function between genders, which is important to consider when examining human fertility (Fig. 2).

Endothelial Dysfunction in Female Infertility

Reproductive health and long-term cardiovascular risk is an emerging area of study. Infertility, often a marker of underlying health issues, has been linked to an increased risk of CVD later in life. Women with prolonged infertility have higher rates of hypertension, hypercholesterolemia, and diabetes, which are key risk factors for CVD. Multiple studies indicate that women who experience infertility may have a higher risk of CVD.

According to the Swedish Medical Birth Register, women who reported at least five years of infertility before a successful pregnancy had a 19% higher incidence of CVD compared to women without a history of infertility.[13] Factors associated with infertility, such as female age, polycystic ovarian syndrome, endometriosis, and metabolic syndrome, are also risk factors for CVD. Women who experience infertility are at a higher risk of developing hypertension, hypercholesterolemia, and diabetes mellitus (DM) compared to those who do not have a history of infertility.[14]

Affecting over 14% of women, infertility is still under-researched in terms of its long-term effects on cardiovascular health, leaving the current data inconclusive. However, reproductive health overall offers critical insights into a woman's long-term cardiovascular risks. Premature ovarian insufficiency (POI), a condition affecting about 3.5% of women worldwide, occurs when ovarian function diminishes before the age of 40.[15] This leads to symptoms like amenorrhea, low sex hormone levels, and elevated gonadotropin levels, contributing to a sharp decline in estrogen. The resulting estrogen deficiency has been associated with an increased risk of CVD and related mortality. While conditions like premature menopause and adverse pregnancy outcomes, such as hypertensive disorders and gestational diabetes, are now

recognized as clear risk factors for future atherosclerotic CVD, the impact of infertility remains less understood.[16]

The relationship between ED and female fertility in humans remains unclear. Research in mouse models indicates that estradiol, a form of estrogen, possesses significant vasoactive properties that extend beyond its traditional role in reproduction. This has led to the intriguing hypothesis that estrogen may play a regulatory role in endothelial functions critical for female reproductive health. However, despite the insights gained from animal studies, more research is needed to fully understand how ED influences fertility in humans.

Polycystic Ovary Syndrome and Endothelial Dysfunction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women, often linked to ovarian dysfunction, obesity, and infertility. PCOS is a condition that can cause difficulties with pregnancy and increase the risk of complications. It is also associated with other health issues, including insulin resistance, depression, obesity, and metabolic issues.[17] PCOS is characterized by a combination of hyperandrogenism, anovulation, and metabolic disorders. This condition may also present with early signs of ED and atherosclerosis.[18,19]

There is growing evidence that ED in PCOS may be tied to resistance to insulin-induced vasodilation, as demonstrated in *in vivo* studies. Women with PCOS are at higher risk for CVD, with elevated levels of C-reactive protein or PAI-1 and a higher prevalence of coronary artery disease. Several studies have found that women with PCOS commonly exhibit ED, insulin resistance (IR), hyperandrogenism, and obesity/adipocyte dysfunction identified as potential contributing factors. Recent studies found the presence of hyperinsulinemia and insulin resistance in PCOS patients. A meta-analysis suggests endothelial dysfunction is common in PCOS patients.[19,20]

Interestingly, while previous research has established a connection between IR and ED, some patients with IR still maintain normal endothelial function, suggesting a more complex relationship. This complexity has led to speculation that hyperandrogenemia, or elevated levels of circulating androgens, might be the primary driver of ED and the increased CVD risk observed in women with PCOS. Despite the link between IR and ED, PCOS patients can exhibit endothelial dysfunction even when glycemia, lipidemia, and blood pressure are normal. Endothelial progenitor cells (EPCs), which are crucial for repairing blood vessels and supporting neovascularization, may also be dysfunctional in PCOS due to associated conditions like hypertension, obesity, and dyslipidemia.

PCOS is notably recognized as a major risk factor for cardiovascular disease (CVD), particularly in patients where hyperandrogenism, abdominal obesity, and insulin resistance are more pronounced. Further research is needed to clarify how these factors interact and contribute to the cardiovascular risks in PCOS.[20–23]

The potential increased risk of CVD in women with PCOS is still a widely debated issue. Many of the clinical characteristics of PCOS are key elements of metabolic syndrome. This syndrome is strongly linked to the formation and progression of CVD. Given the shared risk factors, it is suggested that women with PCOS might be at a higher risk for cardiovascular issues, though the precise relationship continues to be an area of active investigation (Fig. 3). Nevertheless, the epidemiological evidence connecting PCOS to actual cardiovascular events is not convincing (Fig. 4). The elevated cardiovascular risk observed in PCOS is likely partly due to the metabolic disturbances associated with the condition. Dyslipidemia, diabetes mellitus, and obesity are potential cardiovascular risk factors that frequently occur together in women with PCOS.[21,22]

Changes in oocyte quality and endometrial receptivity play a crucial role in the reproductive challenges faced by women with PCOS. In these patients, oocyte competence is often compromised, with disrupted follicle development and abnormal oocyte morphology, which negatively impact the ability of the oocytes to mature and undergo successful fertilization.[24] Additionally, dysregulation of endometrial gene expression in women with PCOS can lead to chronic inflammation, immune system imbalances, and cellular dysfunction. These factors contribute to a higher risk of miscarriage and various obstetric complications, further complicating fertility outcomes.[24,25] The heterogeneous causes underlying PCOS contribute to reproductive problems and infertility. Previous research indicates that androgens contribute to ED in women with PCOS. Estradiol administration can mitigate these effects, although there is no standard guideline for managing endocrine disorders in PCOS.[26]

Endometriosis and Endothelial Dysfunction

Endometriosis is a condition characterized by the presence of endometrial stromal and glandular cells outside the uterine cavity, commonly found in areas like the ovaries, uterine ligaments, and the gastrointestinal system. Women with endometriosis often experience symptoms such as pelvic pain, dysmenorrhea, dyspareunia, and infertility. It is estimated that 30 to 50 percent of women with endometriosis struggle with infertility, while 25 to 50 percent of women presenting

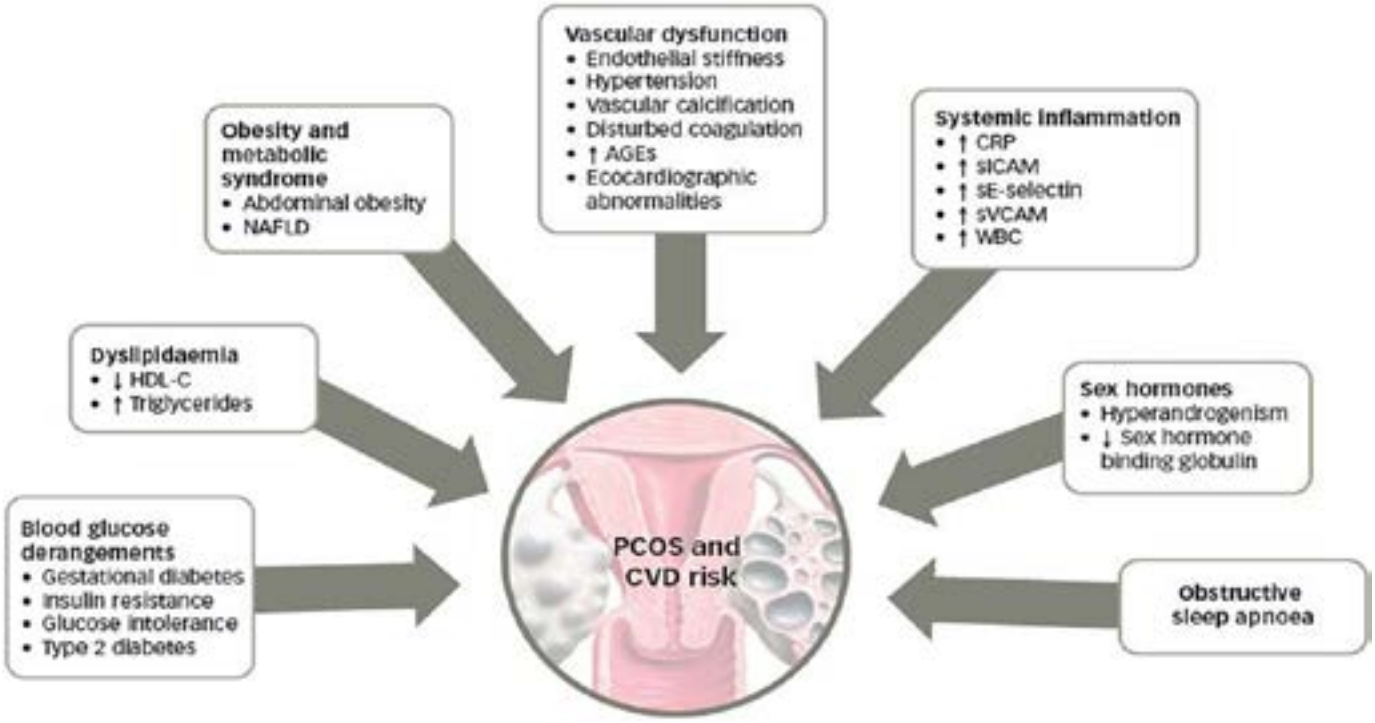

Figure 3. PCOS and CVD risks[21]

↓: Decreased/reduced; ↑: Increased. AGEs: Advanced glycated end-products; CRP: C-reactive protein; sICAM: Soluble intercellular adhesion molecule; sE-selectin: Soluble E-selectin; sVCAM: Soluble vascular cell adhesion protein; WBC: White blood cells; NAFLD: Non-alcoholic fatty liver disease; HDL-C: High-density lipoprotein cholesterol; PCOS: Polycystic ovary syndrome; CVD: Cardiovascular disease

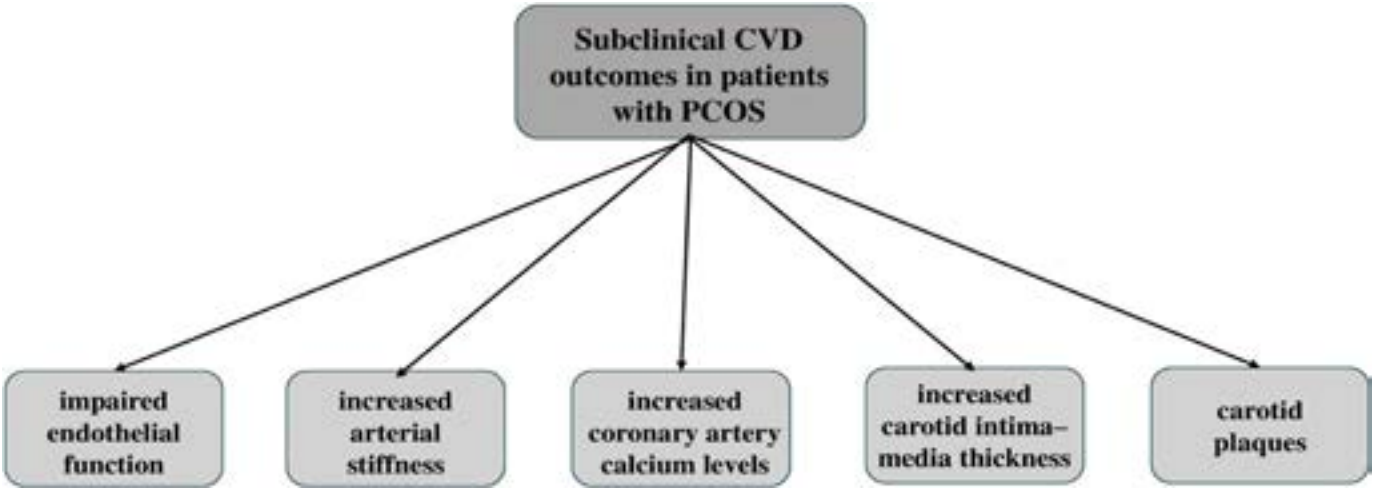

Figure 4. CVD outcomes in women with PCOS[23]

CVD: Cardiovascular disease; PCOS: Polycystic ovary syndrome

with infertility are diagnosed with endometriosis.[27,28] Additionally, this condition has been linked to adverse obstetric outcomes, including preterm birth and low birth weight.[29]

Recent data also demonstrate that endometriosis patients are more prone to have CVD, including myocardial infarction, stroke, and all-cause mortality.[30,31] A proatherogenic profile

and increased subclinical atherosclerosis have been reported, proving a possible association between ED and endometriosis.[32,33] However, further studies are required to explain the risk of CVD in women with endometriosis and the potential benefits of CVD screening tests for these individuals.

CONCLUSION

ED plays a critical role in cardiovascular health and is increasingly recognized for its impact on reproductive outcomes. Extensive research has highlighted the importance of endothelial function in maintaining vascular homeostasis and its intricate relationship with sex hormones such as estrogen and testosterone. While there is substantial evidence linking ED to various cardiovascular diseases, its specific effects on female fertility and reproductive health remain less clear.

Despite advancements in research, the exact mechanisms by which ED affects fertility and the identification of reliable biomarkers for reproductive health remain areas of active investigation. The challenge lies in the multifaceted nature of these conditions, where hormonal imbalances, metabolic disturbances, and endothelial changes intersect. Conditions like PCOS and endometriosis further illustrate the complexity of this relationship. Women with PCOS often face challenges related to ED, which may exacerbate insulin resistance and metabolic issues, potentially increasing their cardiovascular risk. Similarly, endometriosis is associated with adverse reproductive and cardiovascular outcomes, underscoring the need for a deeper understanding of how endothelial health influences both fertility and long-term cardiovascular risk.

In summary, there is a known connection between endothelial health and reproductive parameters, but there are no definitive and suitable markers for fertility and infertility.

Disclosures

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