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Physiological Mechanisms and Intervention Strategies for the Increased Cardiovascular Risk in Perimenopausal Women

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of female mortality worldwide, and risk rises sharply during the perimenopausal transition as circulating estrogen declines. This review synthesizes macro-to-micro physiological mechanisms linking estrogen loss to vascular and cardiac dysfunction, including adverse shifts in blood pressure and lipid profiles, increased arterial stiffness, endothelial nitric oxide (NO) impairment, heightened oxidative stress with mitochondrial dysfunction, pro-fibrotic remodeling, and reduced angiogenic repair capacity. We further discuss how differential signaling through ERα, ERβ, and G protein–coupled estrogen receptor (GPER) contributes to heterogeneous cardioprotective effects across individuals and clinical phenotypes. Current intervention strategies are evaluated, emphasizing additive benefits of lifestyle modification and guideline-directed pharmacotherapies (e.g., statins and antihypertensives) for risk reduction. Hormone replacement therapy (HRT) remains controversial; evidence supports a timing-dependent "critical window" in which early initiation near menopause may confer vascular benefit, whereas late initiation offers limited protection and may increase thrombotic or cerebrovascular risk depending on formulation and route. Finally, we highlight emerging biomedical engineering approaches-particularly AI-enabled risk stratification using electronic health records, wearable data, and imaging biomarkers-as promising tools to enable earlier detection and personalized prevention for perimenopausal women.

KEYWORDS

Perimenopause; Estrogen; Cardiovascular Disease; Endothelial Dysfunction; Arterial Stiffness; Hormone Replacement Therapy; Timing Hypothesis.

1. INTRODUCTION

Cardiovascular disease (CVD) remains the main cause of death for women globally [1]. It causes more deaths than all the combined cancers. Women tend to be less likely to have heart disease than comparable men before they are in menopause. But the protection drops significantly at perimenopause. The perimenopausal phase usually occurs between late 40s and 50s [2].

The falling levels of estrogen are the major cause of this transformation. Estrogen is a hormone that helps to protect your heart in many ways. It controls the tone of blood vessels by stimulating production of nitric oxide. It helps in inflammation and oxidative stress also. It is capable of regulating lipid metabolism and acts for the endothelial repair. The protective effect of estrogen diminishes when estrogen levels drop in perimenopause and after menopause. The consequence of this is physiological adaptations that accelerate the onset of atherosclerosis [3].

There are no great treatment options available to mitigate the increased vascular risk after menopause. These treatments are blood pressure drugs, cholesterol-reducing statins and lifestyle changes. The

evidence of RCTs shows the statin therapy can reduce low-density lipoprotein (LDL) cholesterol and prevent major cardiovascular events in postmenopausal women and the result is significant [4]. Antihypertensive therapy also shows a definite decrease in cardiovascular morbidity associated with reduction of blood pressure. These interventions have been demonstrated to be of benefit across all ages of women, though their effect may be more evident in younger women [5]. Lifestyle changes such as change in diet, regular exercise, and stopping smoking can consistently improve vascular function and imply that their effects are additive, not rehabilitative.

Hormone replacement therapy (HRT) was once viewed as a promising answer to management of CVD risk in postmenopausal women [6]. Its use is currently contentious, particularly based on findings from the Women's Health Initiative (WHI) of increased incidence breast cancer risk with HRT. Recent evidence suggests that the cardiovascular effect of HRT can be definitively ascertained by the timing of initiation of treatment. This concept is known as the "critical window" hypothesis, which proposes that intervention early after menopause can confer cardiovascular benefits [7].

In the last two decades, estrogen signaling research has made great progress. Researchers have not only found the well-known estrogen receptors ERα and ERβ. They also know about the membrane-bound G protein-coupled estrogen receptor. They have also discovered that locally in cardiovascular tissues, estrogen can be synthesized [8]. These discoveries have increased our knowledge about how the cardiovascular system is protected by estrogen, as well as emphasizing the requirement for further research into the molecular mechanisms of estrogen.

This review aims to initially summarize the molecular and physiological mechanisms by which estrogen influences cardiovascular function in women. We subsequently evaluate current evidence for lifestyle and pharmacological treatment. Finally, we look at how state-of-the-art biomedical engineering approaches to augment women at the perimenopausal phase that combines engineering, biology, and medicine to develop new health technologies [9].

2. PHYSIOLOGICAL MECHANISMS: FROM MACRO TO MICRO

Women in the perimenopausal period present with an acute increase in the risk of CVD [10]. This increase is directly related to the reduction in circulating estrogen, a hormone with established cardioprotective action.

Perimenopausal women usually have high blood pressure, unfavorable lipid profile changes as evidenced by increased LDL cholesterol, reduction of high-density lipoprotein (HDL) cholesterol, and triglycerides, with increasingly elevated vascular stiffness due to reduced arterial elasticity [10]. Stiffening of the arteries primarily results from structural changes in the arterial wall, including increased collagen deposition, disrupted elastin fibers, and thickening of the medial wall. All these changes together impair the ability of the vessel to contain pulsatile blood flow. These macro-level shifts both reflect the direct vascular consequence of estrogen deficiency, such as decreased nitric oxide-mediated vasodilation, and the consequences of lifestyle influences typically occurring at menopause, such as decreased physical activity, dietary changes, and weight gain. The overlap of hormonal loss and behavioral risk factors hastens the development of atherosclerosis, coronary heart disease, cerebrovascular disease, and peripheral artery disease, all highlighting the multi-faceted nature of cardiovascular risk in perimenopausal women.

Whereas estrogen deficiency sets off a chain of cellular and molecular abnormalities. Endothelial dysfunction results with the helpful action of estrogen on vasodiation through the eNOS/NO pathway being reduced. In physiological conditions, estrogen preserves eNOS expression and inhibits oxidative stress, thereby ensuring NO availability. Without estrogen, eNOS expression is reduced and reactive oxygen species down-Consume NO. This creates a pathological regulation of vascular tone, disrupting the balance between vasodilation and vasoconstriction and inducing hypertension and

arterial stiffening. Overly susceptible vessels are also more prone to inflammation, leukocyte adhesion, and thrombosis, with acceleration of atherosclerosis.

estrogen deficiency has increased oxidative stress and causes mitochondrial dysfunction. In normal conditions, estrogen preserves the integrity of mitochondria and reduces ROS through the activation of antioxidant enzymes and the closure of the mPTP. Following estrogen reduction, oxidative damage is increased, ATP synthesis is reduced, and heart muscle cell death is enhanced.

Low estradiol in cardiac tissue also increases fibrotic remodeling. Estrogen via ERβ suppresses pro-fibrotic mechanisms such as TGF-β1. Without this suppression, there is increased deposition of collagen with extracellular matrix remodeling leading to subsequent myocardial stiffening and harmful structural remodeling.

Angiogenesis is also impaired as the levels of estradiol fall. Estradiol, via ERα, normally stimulates vascular endothelial growth factor (VEGF) expression and mobilizes endothelial progenitor cells (EPCs) to assist in repairing the vasculature. Impaired levels of estradiol undermine these repair processes, limiting the ability to form new blood vessels in ischemic or hypertrophic heart muscle.

Both prior [11] and current studies [8] illustrate the distinctive roles played by the estrogen receptors in these phenomena. ERα also has pro-angiogenic activity and blood pressure control, while ERβ is largely responsible for antifibrotic action and slowing of pathological matrix remodeling. The G protein-coupled estrogen receptor (GPER) is a transmembrane receptor newly identified and implicated in rapid vasodilation, mitochondrial protection, and mPTP inhibition. Registered, expression of GPER is lower in males and higher in females and, therefore, seems to have a sex-specific function in cardiovascular physiology.

Overall, these protective responses are a consequence of co-activation of genomic and non-genomic signaling pathways. Genomic activation of estrogen receptors increases cardioprotective genes like VEGF and eNOS, while non-genomic signaling through cell membrane-bound ERs and GPER activates kinase pathways like MAPK/ERK and PI3K/Akt. These actions combined preserve vascular balance, improve endothelial function, and encourage mitochondrial survival.

3. VARIABILITY IN ESTROGEN'S CARDIOPROTECTIVE EFFECTS

In normal physiological states, estrogen provides global cardiovascular protection. It stabilizes the electrical activity and modulates the function of ion channels in cardiac tissue, thus lowering the incidence of arrhythmias and preserving normal rhythm of the heart. Estrogen also preserves contractility of myocardium and dampens maladaptive remodeling processes and does all these, which reduce the risk of heart failure.

By metabolic regulation, estrogen lowers LDL cholesterol and increases HDL cholesterol, in addition to increasing sensitivity to insulin and increased peripheral glucose uptake [12]. These metabolic alterations reduce the load of metabolic syndrome, which manifests as the major catalyst of cardiovascular disease.

In the vascular compartment, estrogen induces endothelial release of NO, suppresses vascular smooth muscle proliferation, and reduces oxidative stress damage. These are synergistic effects that augment vasodilation, maintain arterial compliance, and inhibit atherosclerotic plaque development.

Genetic factors determine the magnitude and direction of estrogen responsiveness of an individual. Variation in the genes for the estrogen receptors, i.e., ERα, ERβ, and GPER, regulates receptor expression and the efficiency of signal transduction, which consequently influences lipid metabolism, blood pressure, and vascular remodeling. Turner syndrome or FMR1 premutation are chromosomal abnormalities leading to enhanced susceptibility to premature ovarian failure and subsequent premature estrogen deficiency with associated augmented lifetime cardiovascular risk in females.

Clinical data strongly support the importance of timing of treatment. Data from the Early versus Late Intervention Trial with Estradiol (ELITE) confirm the "timing hypothesis" [13]. In the trial, estradiol therapy was initiated within six years of menopause significantly delayed t carotid intima-media thickness progression compared with placebo ($p = 0.008$), while treatment following over ten years of postmenopause was ineffective ($p = 0.29$) [14]. These findings imply estrogen primarily shields when the vasculature is in relatively good condition; once advanced arterial stiffness and endothelial dysfunction have developed, late estrogen therapy can fail to reverse and may even exacerbate established damage.

Metabolic disorders greatly change the cardiovascular effects of estrogen. Obesity, hypertension, dyslipidemia, and insulin resistance can disrupt estrogen-mediated signaling. A Cochrane systematic review indicated that in relatively healthy postmenopausal women, hormone therapy resulted in only modest cardiovascular risks [15]. Conversely, however, in women with pre-existing cardiovascular disease or metabolic syndrome, combined hormone replacement therapy was associated with increased risks of coronary event and venous thromboembolism. Adiposity in particular promotes chronic low-grade inflammation and oxidative stress and directly interferes with the action of estrogen to maintain nitric oxide bioavailability and vascular compliance.

Clinical conditions of early loss of estrogen play a pivotal role in determining the course of cardiovascular health. Women with premature ovarian failure or premature menopause (before 40-45 years) have abrupt estrogen loss at their otherwise ages of lowest cardiovascular risk [16]. If not treated, they are vulnerable to hastened atherosclerosis, rising rates of coronary heart disease, and lower life expectancy. Current clinical practice guidelines thus recommend hormone therapy at least until the average age of natural menopause to reduce long-term cardiovascular and skeletal effects.

4. HORMONE REPLACEMENT THERAPY (HRT): OPTIONS AND OUTCOMES

Hormone replacement therapy has always served two functions: relief of menopausal symptoms and treatment of the spectacular acceleration of cardiovascular risk following menopause.

Systemic treatment in the form of oral estrogen, most commonly conjugated equine estrogen or 17β-estradiol, is the traditional method and improves lipid profiles. The first-pass hepatic metabolism of this product, however, causes induction of clotting factor, C-reactive protein, and triglyceride synthesis, thereby elevating the risk of thrombosis. Transdermal estrogen given in the form of patches or gels evades liver metabolism and has few impacts on coagulation factors and triglyceride concentrations but maintains favorable vasodilatory and endothelial effects. Local vaginal estrogen, present in the form of creams, tablets, or rings, is primarily aimed at urogenital symptoms. Due to low systemic absorption, it causes little cardiovascular or thrombotic effect and can be regarded as suitable for the systemically high-risk woman. Treatment regimens are further grouped into estrogen-alone or combined estrogen-progestogen therapy. Among progestogens, micronized progesterone and dydrogesterone have better cardiovascular and thrombotic safety profiles compared to synthetic analogs like medroxyprogesterone acetate.

Studies involving several phases have described the cardiovascular effects and risks of HRT. Early observational studies have shown reduced incidence of coronary heart disease with HRT, but randomized trials subsequently demonstrated more complex outcomes. WHI trial found combined therapy to have a hazard ratio of 1.18 (95% CI: 0.95–1.45) for coronary heart disease with no protective effect and a trend towards harm [16]. The same regimen increased overall stroke risk by approximately 31% and ischemic stroke risk by 44% [17]. The Cochrane review also illustrated that over 4 to 6 years of follow-up, oral combined HRT led to 6 additional strokes per 1,000 women (number needed to harm [NNH] = 165), 8 additional venous thromboembolic events per 1,000 women

(NNH = 118), and 4 additional pulmonary embolism events per 1,000 women (NNH = 242), all with statistically significant relative risks [18].

Timing of treatment appears to be especially significant for HRT's effects on the cardiovascular system. The ELITE trial demonstrated directly that estradiol treatment started within six years of menopause greatly suppressed carotid intima-media thickness increase compared to placebo ($p = 0.008$) [13], while starting more than 10 years after menopause was not beneficial to the vasculature ($p = 0.29$). These findings support the "critical window" hypothesis, that estrogen therapy is protective for vascular function if begun early in the postmenopausal years but no longer functions or may be harmful after atherosclerosis has developed. These observations are capable of explaining heterogeneity between observational studies that recruited mainly younger women near menopause and subsequent randomised trials enrolling older women further from menopause.

Uncertainty continues as to the optimal form and route of delivery in the balance between cardiovascular protection and breast cancer, venous thromboembolism, and stroke risk. The transdermal vs. oral route choice is particularly relevant in women with metabolic syndrome, obesity, or a history of increased thrombosis risk, in whom transdermal estrogen may be safer. For premature ovarian failure or premature menopause in women, guidelines are to apply HRT to the age of natural menopause to reduce long-term cardiovascular and skeletal complications. But in elderly postmenopausal women, especially those who start therapy more than a decade after menopause, HRT is not indicated for primary or secondary prevention of cardiovascular disease.

5. LIFESTYLE AND PHARMACOLOGICAL INTERVENTIONS

Lifestyle modification is a part of cardiovascular risk reduction in postmenopausal women. This strategy is extremely effective on several health indices. It particularly increases lipid levels. It also sustains blood pressure levels. It also improves metabolic health in general. There is a significant amount of evidence that substantiates the value of systematic exercise programs. A randomized controlled multicenter 26-week trial treated sedentary postmenopausal women [19]. Women were provided an intensive exercise program with resistance training. The multi-factorial intervention induced measurable improvements, such as lipid favorable responses and lowering of blood pressure. Systematic reviews are also evidence. Regular aerobic exercise produces large blood pressure improvements with systolic pressure lowered by 5-8 mmHg and diastolic pressure lowered by 3-5 mmHg. Combined training techniques have unique advantages. Aerobic and resistance exercise combined optimize heart rate variability [20]. The mechanisms behind include improved endothelial function through upregulation of NO production, improved hemodynamic values, and metabolic regulation through visceral fat reduction and insulin sensitivity enhancement [20].Medications are sometimes required, especially for women with higher cardiovascular risk. Statins (HMG-CoA reductase inhibitors) are the mainstay of lipid-lowering therapy. The 2022 U.S. Preventive Services Task Force (USPSTF) recommends statin use for adults aged 40-75 with ≥ 1 cardiovascular risk factor and a 10-year ASCVD risk $\geq 10\%$ [21]. Meta-analysis of the 12 randomized trials ($\approx$ 85,816 participants) demonstrated that statins reduce the risk of myocardial infarction (RR 0.67, 95% CI 0.60-0.75), stroke (RR 0.78, 95% CI 0.68-0.90), and all-cause mortality (RR 0.92, 95% CI 0.87-0.98) [21]. In a reanalysis of the HERS trial [22], postmenopausal women using statins for ≥ 3 years experienced a 26% lower risk of coronary events compared with non-users. In a Korean cohort of postmenopausal women at moderate-to-high risk, atorvastatin 20-40 mg daily for 16 weeks lowered LDL cholesterol by 45.8% ± 16.7 and total cholesterol by 33.2% ± 10.9 [23].

Blood pressure-lowering medications such as ACE inhibitors, ARBs, beta-blockers, and calcium-channel blockers are crucial in controlling hypertension, a key risk factor for stroke and heart failure. A large meta-analysis by Ettehad et al. [24] found that every 10 mm Hg reduction in systolic blood pressure reduces major cardiovascular events by about 20%, coronary heart disease by 17%, and stroke by 27%. Another meta-analysis focusing on patients with prior stroke or transient ischemic

attack (TIA) reported that more intensive blood pressure lowering reduced recurrent stroke risk (RR 0.83, 95% CI 0.78-0.88) [25].

There is also emerging evidence that statins may mitigate some of the thromboembolic risk from hormone therapy. A large population-based case-control study (n = 223,949 women, age 50-64) found that hypertensive users taking statins had an 18% lower risk of venous thromboembolism (VTE) compared with hypertensive users not taking statins (OR 0.82, 95% CI 0.71-0.94) [26].

Together, combining healthy lifestyle habits with appropriately selected medications including statins, antihypertensives, and indicated glucose-lowering drugs yields the largest and most durable reduction in cardiovascular risk after menopause.

6. EMERGING TECHNOLOGIES: BIOMEDICAL ENGINEERING PERSPECTIVES

Advances in machine learning (ML) and artificial intelligence (AI) are bringing new avenues of cardiovascular risk stratification in females. More access to diverse data related to health enables more provision of accurate prevention interventions. Data sources are electronic health records and wearables for consumers. The data can be processed effectively with powerful analytical tools.

AI methods perform well while dealing with such complex multidimensional data. AI tools integrate data from diverse sources effectively. AI integrates activity tracker and digital health device data in primordial prevention. This helps to identify patients with developing early risk factors. The risk factors in this case are dyslipidemia and hypertension. Clinical and imaging data add even more precision to predictive risk. AI algorithms combine these types of data with the goal of guiding early intervention. In women with known CVD, the same technology identifies candidates for upgrading treatment. It also helps to identify patients for digital rehabilitation. This enables more personalized management plans. An individualized plan over a lifetime remains the most important way to reduce cardiovascular risk in women. Prevention and screening should be directed to various physiological stages. The most opportune points are the critical points.

As women make their way through midlife and menopause, the prevention focus changes to atherosclerotic cardiovascular disease. Continuous risk stratification becomes critical and screening for established risk factors has to be performed, for instance, hypertension and hyperlipidemia. North American Menopause Society has incorporated atherosclerotic cardiovascular disease risk scoring into clinical decision support systems. This will help clinicians evaluate cardiovascular risk as part of the process of making decisions regarding postmenopausal hormone therapy [15]. Tools like My Life Check enable women to know their cardiovascular status. They provide individualized recommendations for change [27]. Digital technologies enhance preventive services availability. For example, AI-powered chatbots, virtual visits, and home remote monitoring systems can integrate health management into everyday life and reduce care barriers [28].

Increasingly diverse health information is generated by older women. AI is able to tap such information for individualized risk stratification. Routine mammography sometimes identifies breast arterial calcifications. Breast arterial calcifications have associations with cardiovascular outcome. Neural networks currently enable automatic quantification of such calcifications [29]. Because of the high usage of mammography in older women, this imaging modality is promising for CVD risk screening. It improves plaque characterization and risk stratification. Imaging modalities include computed tomography and echocardiography. Magnetic resonance imaging is also improved with AI analysis.

7. CONCLUSION

Perimenopausal women are faced with increasing cardiovascular risk due largely to estrogen decline. This decrease in hormones results in endothelial dysfunction, metabolic derangements, and vascular remodeling that together increase atherosclerosis. Evidence supports that estrogen's cardioprotective effect is time-dependent, confirming the "timing hypothesis" for hormone therapy. Besides hormones, lifestyle and pharmacologic interventions provide complementary risk reduction. Wearable sensors and advanced algorithms represent new technologies enabling early detection and individualized management. Integration of biological knowledge, clinical practice, and engineering innovation offers a comprehensive approach to maintaining women's cardiovascular health during and after the menopause transition.

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