

The impact of female sex hormones on cardiovascular disease: from mechanisms to hormone therapy

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ABSTRACT Cardiovascular disease remains the leading cause of mortality in women, yet it has not raised the awareness from the public. The pathogenesis of cardiovascular disease differs significantly between females and males concerning the effect of sex hormones. Estrogen and progestogen impact cardiovascular system through genomic and non-genomic effects. Before menopause, cardiovascular protective effects of estrogens have been well described. Progestogens were often used in combination with estrogens in hormone therapy. Fluctuations in sex hormone levels, particularly estrogen deficiency, were considered the specific risk factor in women's cardiovascular disease. However, considerable heterogeneity in the impact of hormone therapy was observed in clinical trials. The heterogeneity is likely closely associated with factors such as the initial time, administration route, dosage, and formulation of hormone therapy. This review will delve into the pathogenesis and hormone therapy, summarizing the effect of female sex hormones on hypertension, pre-eclampsia, coronary heart disease, heart failure with preserved ejection fraction, and cardiovascular risk factors specific to women.

Regardless of gender identity, cardiovascular disease (CVD) remains the leading cause of death for decades.^[1] Women tend to have an average 5-year longer life expectancy than men and experience a lower mortality risk across all age groups.^[2] Despite this extended lifespan, women still face a greater risk of cardiovascular death at their late life period.^[3] Most clinical trials often included a much larger proportion of men than women, and guidelines were formally developed based on this male-dominated evidence. Findings from male-dominated population doesn't apply to female in many cases. Therefore, it's substantial to raise awareness of CVD in women.

Female sex hormones result in a complex effect on cardiovascular system, contributing to the gender differences in CVD. Premenopausal women experience a significantly lower risk of CVD compared to both postmenopausal women and age-matched males.^[4,5] Meanwhile, postmenopausal women face an increased risk of CVD compared to their premenopausal counterparts of the same age.^[6] However, the potential cardiovascular benefit of endogenous sex hormones is not consistent with the results of hormone therapy. Current hypothesis suggests th-

at the deficiency of female sex hormones explains the increased cardiovascular risk in women, while the heterogeneity of postmenopausal hormone therapy efficacy may be related to factors such as initiation time, duration, administration route, formulation, and dosage (Figure 1).

FEMALE SEX HORMONES AND SIGNAL PATHWAYS

Sex hormones in women are mainly synthesized and secreted by the ovaries, including estrogen, progesterone and small amounts of androgens. Estrogens comprise a group of hormones consisting of 17β-estradiol (E2), estrone (E1), estriol (E3) and estetrol (E4, only exists during pregnancy).^[7] E2 is the primary form of estrogen in premenopausal women and is also the most biologically active estrogen. E2 and its derivatives constitute the primary components of estrogen therapy. E1 typically becomes the major source of estrogen after menopause. E3 is the final metabolic product of E2 and E1, and its activity is exceedingly weak, primarily secreted in large quantities during pregnancy. In the normal physiological cycle of women, the levels of sex hormones vary in differ-

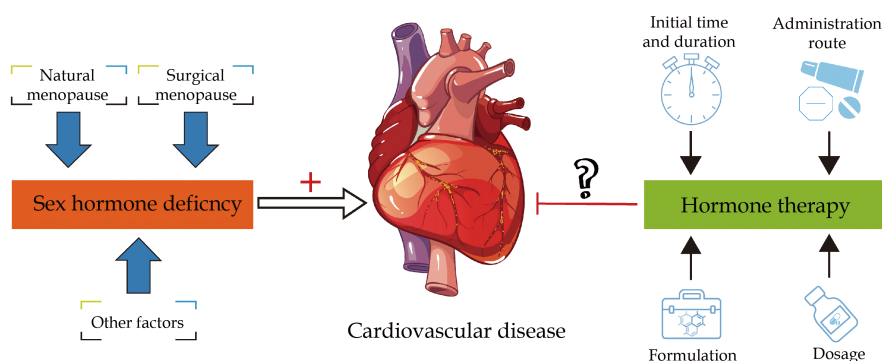


Figure 1 Association between female sex hormone and cardiovascular disease.

ent periods. Estrogen presents in higher levels in females from adolescence to menopause, while in postmenopausal women, estrogen levels are comparable to those of age-matched men.^[8]

Sex hormones make their impact on cardiovascular system through genomic and non-genomic effects.^[9,10] Aromatase (a type of CYP450 enzyme) catalyzes the conversion of testosterone to estrogen.^[11] The impact of estrogen is mediated through nuclear and membrane estrogen receptors (ER), including estrogen receptor alpha (ER α), estrogen receptor beta (ER β), and G-protein-coupled ER (GPR30 or GPER). In terms of genomic effects, E2 binding to the ER induces the formation of homo/hetero dimers, translocation to the nucleus, and direct interaction with estrogen response elements or transcription factors, which regulates the expression of target genes. Meanwhile, E2 initiate rapid non-genomic effects by binding to ERs at the plasma membrane, thereby activating signaling pathways such as phosphoinositide 3-kinase, mitogen-activated protein kinase/extracellular signal-regulated kinase, and cyclic adenosine monophosphate. Additionally, E2 binds to mitochondrial membrane-localized ERs, reducing reactive oxygen species production and enhancing cell survival.^[10]

Progesterone receptors are categorized into the nuclear progesterone receptors (PR) and membrane-bound PRs. The genomic effects of progesterone are mediated by nuclear PRs, including PR-A, PR-B, and PR-C (confirmed to be expressed in breast cancer cells). Progesterone modulates various physiological processes through non-genomic effects by binding to membrane-bound PRs, including membrane-bound progesterone receptors, progesterone receptor membrane component 1, and GABA-A receptors, which impacts growth receptor signaling pathways, mitogen-activated protein kinase pathways and activates tyrosine kinase Src.^[12]

HYPERTENSION

Hypertension is considered one of the most common chronic diseases worldwide and is a major risk factor of CVDs.^[13,14] Estrogen plays a role in promoting vasodilation through endothelial-dependent effects involving both ER and GPR30.^[15] Animal studies provide compelling evidence regarding estrogen's effect on blood pressure (BP) and CVD.^[16-20] The impact of estrogen on the renin-angiotensin-aldosterone system (RAAS) remains complex. On one hand, estrogen promotes the circulating levels of angiotensinogen and aldosterone to upgrade RAAS activity. On the other hand, estrogen inhibits the activity of angiotensin converting enzyme, which consequently reduce the formulation of angiotensin II, increase the formation of Ang-(1-7) and enhance the effect of bradykinin.^[21] The bi-directional effects of E2 on RAAS finally result in the antihypertensive effect. Additionally, estrogens modulate BP directly through non-genomic effects on vascular, renal and cardiac cells by reducing calcium efflux. And it indirectly downgrades the expression of endothelin-1 and catecholamines, contributing to vasodilatory effect.^[22,23] Progesterone is a potent aldosterone antagonist, exerting its action on the mineralocorticoid receptor to inhibit sodium and water retention.^[24]

After menopause, an increased sensitivity to salt has been observed in females.^[25-27] This heightened sensitivity is attributed to the lower estrogen levels post-menopause, which are associated with the upregulation of RAAS and the sympathetic nervous system. Additionally, reduced vascular nitric oxide bioavailability is also linked to the decline in estrogen levels.^[28]

There is a time-dependent association between women's BP and estrogen levels. During the luteal phase, characterized by elevated estrogen levels, women tend to have lower BP compared to the follicular phase of the men-



strual cycle.^[29] Before menopause, endogenous estrogen inhabits the progression of hypertension.^[5,25] After menopause, estrogen levels in women drop significantly. This aligns with the lifelong BP trend in women, where from the age of 13 years old, both systolic BP and diastolic BP are lower than those in men. However, after the age of 60 years old, women's risk of hypertension surpasses that of men, becoming notably higher.^[30] While premenopausal women typically show a lower prevalence and reduced severity of hypertension, the risk of hypertension undergoes a significant transformation post-menopause.^[3,31]

Considerable evidence supports the association of endogenous estrogen with decreased BP in women.^[5,32] Consequently, the administration of exogenous estrogen might reasonably be expected to have a similar BP-lowering effect. However, the impact of exogenous estrogen treatment on BP in humans has yielded inconsistent findings.^[33–41] This disparity appears to be influenced by formulation, dosage, and the methodology employed for BP measurement.^[42]

Previous studies focusing on normotensive postmenopausal women has shown that BP reductions were associated with the use of transdermal estrogen but not with oral estrogen.^[43–47] The Women's Health Initiative Observational Study, which included 19,986 normotensive patients using menopausal hormone therapy (MHT), found that when compared to conjugated equine estrogen (CEE) with or without a progestin, the risk of newly treated hypertension was lower in women who used transdermal estradiol or oral estrone sulfate dominant preparations.^[44] Similarly, a prospective population-based study conducted in France among normotensive women using MHT reported that the risk of hypertension increased with the use of oral estrogen, especially when combined with progestogen, but not with transdermal estrogen.^[43] These heterogeneity in hypertension risk observed in relation to the route of estrogen administration may be attributed to differences in pharmacokinetics. Oral estrogen undergoes first-pass hepatic metabolism, which has been postulated to activate RAAS.^[45,48,49]

Recently, a cohort study exploring the relationship between the route of administration, formulation, duration of use, and cumulative dose of estrogen and the risk of postmenopausal hypertension has yielded important findings.^[50] It revealed an association between oral estrogen therapy and an increased risk of hypertension in women. In postmenopausal women receiving estrogen therapy, the lowest risk of hypertension was observed with the

use of non-oral estradiol at the lowest effective dose and for the shortest duration. This suggests that minimized risk of hypertension may be achieved by using non-oral estradiol, at the lowest effective dose, and for a shorter duration.

Drospirenone (DRSP), derived from 17- α -spiro-lactone, combines the therapeutic effects of progestogens, anti-mineralocorticoids, and anti-androgens.^[51,52] In China, a 3 mg dosage of DRSP is commonly used in combination with ethinyl estradiol as a combined oral contraceptive. The anti-mineralocorticoid effects of 3 mg of DRSP are comparable to those of 25 mg of spironolactone.^[53] Compared to traditional estrogen-progestin therapies, DRSP can counteract the water and sodium retention triggered by estrogen-induced RAAS activation. This may potentially mitigate estrogen-related weight gain and lower BP, especially in hypertensive postmenopausal women.^[54–56] A retrospective analysis revealed that continuous, long-term treatment with DRSP 2 mg/E2 1 mg notably reduced 24-hour systolic BP and diastolic BP, consequently lowering the risk of CVD in early menopausal women with stage 1 hypertension.^[57] This underscores the potential cardiovascular benefits of timely MHT in postmenopausal women.

MHT was commonly recommended in appropriate patients for management of menopausal symptoms. Aside from its cardiovascular effects, MHT also showed favorable or adverse effects on multiple systems. An umbrella review revealed that MHT was associated with reduced risks of bone fracture, diabetes mellitus, and esophageal, gastric, and colorectal cancer.^[58] However, it was linked to increased risks of stroke, venous thromboembolism, gallbladder disease, as well as breast and ovarian cancer. The Women's Health Initiative trial demonstrated that the combination of CEE and medroxyprogesterone acetate elevated the risk of breast cancer while CEE alone therapy resulted in a reduced risk.^[59,60] Therefore, these additional risks should be taken into consideration when implementing hormone therapy.

PRE-ECLAMPSIA

Pre-eclampsia is an intricate disease with multisystem disorder, diagnosed by the sudden onset of hypertension occurring after the 20th week of gestation, accompanied by at least one associated complication. For decades, pre-eclampsia represents one of the leading causes of maternal and fetal mortality globally.^[61] Women who survive



pre-eclampsia are at an elevated risk of long-term health problems, including a reduced life expectancy and increased susceptibility to conditions such as stroke, CVD, and diabetes mellitus.^[62,63]

In animal models, estrogen may exert its effects by preventing inflammation, upregulating Ca^{2+} -activated K^{+} channels, activating GPR30 to stimulate endothelial NO synthase and AKT signaling in endothelial cells, and modulating vascular endothelial growth factor receptor 2 to maintain the normal perfusion of the uterus during pregnancy.^[64] Administration of exogenous E2 is known to inhibit inflammatory mediators, lower BP, and reduce albuminuria.^[65,66] Progesterone also plays a crucial role in the pathogenesis of pre-eclampsia. Pei, *et al.*^[67] found that progesterone can enhance the invasion and inhibit the apoptosis of trophoblasts. Recently, progesterone is considered to promote trophoblast cell invasion ability by activating the phosphatidylinositol 3-kinase/AKT signaling pathway. This effect reduced the progression of pre-eclampsia in pregnant rats in a concentration-dependent manner.^[68]

Previous studies found that patients with pre-eclampsia tend to hold a lower level of estrogen and progesterone.^[69–71] Alternation in enzyme activities, including decrease in 17 β -hydroxysteroid dehydrogenase type 1, aromatase, and catechol-O-methyltransferase, may be associated with declines in estrogen.^[72–74] A meta-analysis involving 6439 patients from nine studies revealed that progestogen supplement before the 20th week of pregnancy in spontaneously achieved singleton pregnancies significantly reduce the risk of pre-eclampsia.^[75] This underscores the potential of using progesterone in the prevention of pre-eclampsia. In summary, estrogen and progestogen plays a pivotal role in the pathogenesis of pre-eclampsia, which suggests the potential of exogenous hormones as a therapeutic agent for managing pre-eclampsia.

CORONARY HEART DISEASE (CHD)

Women tend to experience poorer prognosis compared to men when they present with CHD,^[76] and suffered a higher risk of mortality.^[77] The administration of exogenous estrogen has a significant impact on cardiovascular system, including but not limited to the regulation of cholesterol metabolism and BP.^[42,78,79]

The cardioprotective effect of hypertension has been discussed above. In terms of cholesterol metabolism reg-

ulation, estrogens affect triglycerides and low-density lipoprotein cholesterol (LDL-C) metabolism through multiple mechanisms, such as upregulating low-density lipoprotein receptor expression in the liver,^[80,81] downregulating hepatic lipase,^[82] and proprotein convertase subtilisin/kexin type 9.^[83] Besides, estrogen can influence the progression of atherosclerosis by its effects on endothelial cells, smooth muscle cells, immune cells, and modulating inflammation.^[84]

Menopause is well-established in leading to alterations in serum lipid profiles. Postmenopausal women typically experienced higher levels of total cholesterol (TC), LDL-C, triglyceride (TG), apolipoproteins B and the TC/high-density lipoprotein cholesterol (HDL-C) ratio, alongside reduced HDL-C levels, but no changes of lipoprotein (a) levels when compared to their premenopausal counterparts.^[85–87] These lipid profile changes primarily occur during the perimenopausal period.^[87] An analysis of a community-based women's registry in China has reported similar results, particularly during the late perimenopausal stage.^[88] MHT resulted in an increase in HDL-C levels and a decrease in LDL-C and TC levels.^[89,90] DRSP/E2 combination therapy significantly decreased levels of TC, LDL-C, and apolipoproteins B, while elevating concentrations of HDL-C and apolipoproteins A.^[57] However, oral estrogens were associated with elevated TG, while transdermal E2 was found to reduce TG. The administration route of estrogen and the specific progestogen used played a significant role in determining the varied effects of MHT on lipid profiles.^[90]

It remains uncertain whether the effects of exogenous estrogen in animal models align with that in the human body. Moreover, the theory that sex difference in cardiovascular risk is predominantly related to the presence of estrogen has been challenged. Limited positive effects of estrogen replacement in postmenopausal women were observed and the some excess risks were even highlighted.^[91–94]

The timing hypothesis attempted to explain the reason for the heterogeneity of MHT efficacy.^[95] It comprises two key components. The first component posits that MHT initiated during the perimenopausal transition or early menopause, a period when atherosclerosis is typically in its early stages characterized by fatty streaks or uncomplicated plaques, can prevent the progression of lesions from being larger and more complicated. The second component suggests that the favorable effects of MHT may diminish several years after menopause, by which time at-



therosclerosis has advanced to the complicated plaque stage. Moreover, during this stage, MHT could potentially induce plaque instability, thereby increasing the risk of adverse cardiovascular events. When atherosclerotic plaques exist in coronary arteries, oral estrogen stimulates the production of matrix metalloproteinases, which plays a role in dissolving a portion of the plaque, leading to plaque instability. This instability can potentially result in plaque rupture and thrombosis.^[96]

Nurses' Health Study, a prospective cohort study, notably reported the association between estrogen therapy with decreased risk in CHD and mortality.^[97] Randomized controlled trials on the secondary prevention of CVD, such as the Heart and Estrogen/Progestin Replacement Study, did not demonstrate an overall cardiovascular benefit but rather showed a trend of increased risk for adverse cardiovascular events.^[92] Similarly, investigations on the primary prevention of CVD, known as the Women's Health Initiative trial, did not yield active results.^[98,99] It's worth noting that in the subgroup analysis of women aged 50–59 years in the Women's Health Initiative trial, the use of CEE alone was associated with a reduced risk of CHD, while the combination of CEE with medroxyprogesterone acetate showed a trend of increased CHD risk. The Early versus Late Postmenopausal Treatment with Estradiol trial investigated the use of oral estradiol in combination with vaginal progesterone in women who were either less than 6 years or more than 10 years post-menopause. MHT was associated to a reduced progression of subclinical atherosclerosis (measured by carotid intima-media thickness) when MHT was initiated within 6 years after menopause. However, this benefit was not observed when MHT was initiated 10 years or more years after menopause.^[100] Currently, most clinical guidelines do not encourage the use of MHT for primary or secondary prevention of CVD. However, The International Menopause Society has proposed that in women under the age of 60 years old, who are recently menopausal and without history of CVD, the initiation of estrogen-alone therapy can reduce the risk of CHD and all-cause mortality.^[101]

HEART FAILURE WITH PRESERVED EJECTION FRACTION (HFpEF)

Heart failure with an ejection fraction of $\geq 50\%$ is categorized as HFpEF, while left ventricular (LV) diastolic dysfunction is marked by slow LV relaxation and increas-

ed LV stiffness.^[102] An epidemiological survey conducted in Europe revealed that the incidence of HFpEF is notably higher in women across all age groups, with a particularly pronounced difference observed among elderly patients.^[103] According to data from the China Cardiovascular Association Database-Heart Failure Center Registry, female with HFpEF tend to be older and have poorer prognosis compared to male.^[104]

Effect of E2 on RAAS has been described in "hypertension" part. Furthermore, E2 inhibits the production of reactive oxygen species induced by RAAS and attenuates angiotensin-induced leukocyte recruitment via nitric oxide (NO).^[105]

Natriuretic peptides, such as atrial natriuretic peptide (ANP) and B-type natriuretic peptide, are primarily synthesized and released from the atrial and ventricular myocardium, leading to diuretic and vasodilatory effects. In failing hearts, previous studies have shown that E2 can stimulate the production and secretion of ANP and B-type natriuretic peptide in cultured cardiomyocytes.^[106] E2 has also been found to upregulate the ANP gene, which helps attenuate phenylephrine-induced cardiomyocyte hypertrophy.^[107] Consistent with estrogen levels, ANP levels were reported to be significantly higher in younger women compared to younger men, while no sex difference was observed in older individuals.^[108] Recent studies have shown a strong association between exogenous E2 and natriuretic peptide levels.^[109,110] In the subgroup analysis of the PARAGON-HF study, sacubitril/valsartan was found to improve heart failure prognosis only in female patients compared to the valsartan group.^[111] Considering the elder age of the participants in the PARAGON-HF study (mean age: 72.7 years old), this result may be associated with estrogen deficiency in postmenopausal women and the consequent decrease in natriuretic peptide levels.

LV remodeling and the progression of cardiac dysfunction are linked to the homeostasis of the extracellular matrix (ECM). E2 plays a role in regulating the synthesis of collagen.^[112,113] LV stiffness has been closely associated with fibrillar collagen and cross-linking. Increased deposition and cross-linking of ECM components in the myocardium contribute to myocardial stiffness, which is crucial in the pathogenesis of HFpEF.^[114] Decreased circulatory levels of E2 may contribute to the increases in cardiac ECM components in postmenopausal women.^[115]

E2 can reduce oxidative stress levels in premenopa-



usual women.^[116] Endothelial dysfunction is associated with increased systemic oxidative stress and vascular inflammation, characterized by reduced vasodilators modulating vascular tone, such as NO. E2 plays a role in regulating the production of NO through tetrahydrobiopterin, an essential cofactor for endothelial NO synthase, whose activity is key in LV remodeling and diastolic dysfunction.^[117] The deficiency of estrogen leads to a reduction of NO in postmenopausal women, but this can be prevented through MHT.^[118] Additionally, E2 may regulate systemic and localized persistent inflammation through various pathways by reducing endothelin-1 and pro-inflammatory cytokine levels, repressing NFκB activity, and reducing abdominal fat.^[119]

Collectively, E2 may protect against the development of HFpEF by the regulation in RAAS, natriuretic peptides, ECM, oxidative stress and endothelial dysfunction, and inflammation. Elderly and female individual are more prone to LV diastolic dysfunction.^[120] Estrogen deficiency promotes LV hypertrophy, resulting in smaller LV dimensions and remaining better indices of systolic function, which may contribute to the increased prevalence of high HFpEF in postmenopausal women. MHT can counteract these effects, improving parameters associated with LV diastolic dysfunction^[121,122] and reducing LV mass^[123,124] in postmenopausal women.

The timing hypothesis also applies to patient with the HFpEF to a degree. Animal experiments have supported that early (1 month) estrogen therapy in ovariectomized monkeys can improve LV diastolic function, modulate myocardial gene expression, and exert anti-inflammatory effects,^[125,126] whereas late (4.5 years) estrogen therapy fails to produce these effects. This suggests the potential benefits of early MHT for female HFpEF patients.

CARDIOVASCULAR RISK FACTORS ASSOCIATED WITH FEMALE SEX HORMONES

Since adolescence, cardiovascular risk factors associated with female sex hormones have been present throughout women's life, such as preterm delivery, long/irregular menstruation, oral contraceptives, polycystic ovary syndrome, surgical menopause, premature ovarian insufficiency, shortened reproductive lifespan, and premature/early menopause (Figure 2).

Oophorectomy and Premature Ovarian Insufficiency (POI)

An analysis involving 282,722 premenopausal women in China, indicated that women who underwent hysterectomy and oophorectomy had a higher risk of stroke and ischemic heart disease compared to their age-matched counterparts who did not undergo surgery.^[127] It was previously hypothesized that the lack of estrogen due to menopause or ovarian dysfunction was equally responsible for this increased risk. However, despite a reduced risk when compared to hysterectomy with bilateral oophorectomy, women who had a hysterectomy while retaining ovarian function still experienced a higher risk of CVD. This could be linked to the loss of feedback mechanisms from hystera to ovaries.

Previous studies have consistently reported a correlation between POI and an increased risk of CVD.^[128,129] Furthermore, chemotherapy is recognized as a potential contributor to the development of ovarian failure. Subgroup analysis of the Canadian Longitudinal Study on Aging revealed that women diagnosed with POI faced higher 10-year Framingham risk score compared to those who experienced natural menopause at the expected age, and this risk was comparable to women who had undergone

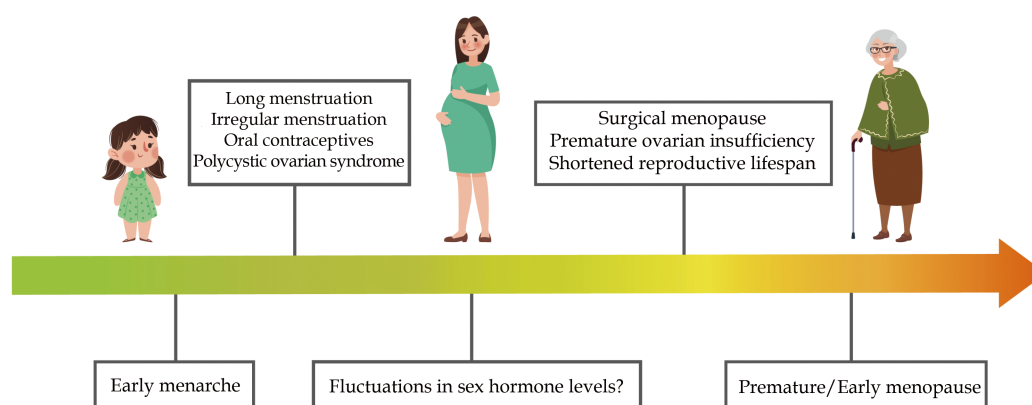


Figure 2 Cardiovascular risk factors related to female sex hormone.



surgical menopause.^[130] For women with POI or premature/early menopause, universal recommendations suggest that patients without contraindications, elevated CVD and breast cancer risks should promptly initiate hormone therapy upon diagnosis and continue it until the expected age of natural menopause.^[131–135]

Abnormal Menstruation

Abnormal menstruation, characterized by early or late menarche, long or irregular menstruation, and polycystic ovarian syndrome, is associated with adverse cardiovascular prognosis. Early menarche is associated with an increased risk of future metabolic syndrome and CVDs.^[136–138] The Million Women Study revealed a U-shaped relationship between the age of menarche and the risk of CHD. The risk of CHD increased significantly when menarche occurs before the age of 10 years old or after the age of 17 years old.^[139] Long or irregular menstrual cycles are believed to be associated with reduced exposure to estrogen, which might contribute to an increased risk of CVD. A pooled analysis of 301,438 patients demonstrated that premature menopause is strongly associated with an increased risk of non-fatal CVD.^[140] Shortened reproductive lifespan is reported to be strongly associated with increased CVD risk in both natural and surgical menopause women.^[128] Shortage of endogenous estrogens may be responsible for these results.

Oral Contraceptive (OC)

Numerous clinical trials have reported the impact of OC on cardiovascular events. However, the findings are inconsistent and even contradictory in some studies.^[141–146] The new generation of OCs contains lower content of ethinyl estradiol ($\leq 30 \mu\text{g}$) compared to older formulations, implying that past studies might have overestimated the cardiovascular risks associated with OCs use. A cohort study in Denmark found that the use of ethinyl estradiol is associated with an increased risk of stroke and myocardial infarction,^[147] with the risk being lower for $20 \mu\text{g}$ compared to $30\text{--}40 \mu\text{g}$.^[144,147] Analysis of the UK Biobank (UKB) cohort indicated that OCs is linked to increased risk of stroke, particularly in the initial year of use.^[148] In contrast, after excluding patients with MHT, the UKB reported favorable results that patients who have previously used OCs intends to obtain a significant net benefit in cardiovascular primary prevention. This association becomes more pronounced in patients who have used OCs for longer durations ($P_{\text{trend}} < 0.001$).^[149] It's worth noting that the UKB

did not record detailed information such as dosage and formulation of OCs. Further studies focus on the impact of dosage, formulations, and duration may be a new direction.

Female Sex Hormone and Spontaneous Coronary Artery Dissection (SCAD)

Approximately 90% of SCAD occurs in females, and it remains an important cause of myocardial infarction related to pregnancy.^[150,151] Patients with SCAD tend to present fewer traditional cardiovascular risk factors than those with typical atherosclerosis. Current evidence suggests an underlying association between fluctuations in sex hormone levels and SCAD. Awareness should be raised when facing patient with fluctuations in sex hormone levels.

Other Cardiovascular Risk Factors

A recent meta-analysis has demonstrated that breastfeeding is linked to a reduced maternal cardiovascular risk, including CHD, stroke, and fatal CVD.^[152] This effect is believed to be closely associated with prolactin and oxytocin.^[153] Oxytocin has been identified not only as promotive for milk ejection but has also been shown benefits on lowering BP, inducing vasodilation, exerting antidiabetic and antioxidant effects, inhibiting inflammation, and reducing fat mass.^[154,155] Although some inconsistencies about dose-response relationships and strength of the association exist, the 2021 scientific statement of the American Heart Association on cardiovascular disease prevention in women declared that “lactation and breastfeeding may lower a woman’s later cardiometabolic risk”.^[156]

CONCLUSIONS AND PERSPECTIVES

Currently, sex hormone is predominantly applied for MHT, menstrual cycle regulation, and contraception. Estrogen therapy is commonly used in perimenopausal women experiencing vasomotor symptoms. Estrogens have a dual impact on the cardiovascular system, with an overall favorable effect in premenopausal women. Progestogens competitively antagonize aldosterone, thereby inhibiting sodium and water retention. Fluctuations in hormone levels, particularly estrogen deficiency, are considered the main underlying factor contributing to the progression of CVDs in women. However, the cardiovascu-



lar protective role of hormone therapy has not been conclusively validated in clinical trials. On the contrary, to some extent, some adverse effects have been observed. This heterogeneity appears to be closely associated with initial time, administration route, dosage, formulation, and duration. Future studies are still necessary to investigate the impact of these factors while taking adverse events such as increased risk of breast cancer and venous thromboembolism into consideration. Additionally, the potential cardiovascular benefits of progestogen and estrogen-progestin therapy for patients in specific period such as pregnancy, deserve further investigation.

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REFERENCES

- [1] Vogel B, Acevedo M, Appelman Y, *et al.* The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet* 2021; 397: 2385–2438.
- [2] Austad SN, Bartke A. Sex differences in longevity and in responses to anti-aging interventions: a mini-review. *Gerontology* 2015; 62: 40–46.
- [3] Benjamin EJ, Blaha MJ, Chiuve SE, *et al.* Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 2017; 135: e146–e603.
- [4] Mendelsohn ME. Protective effects of estrogen on the cardiovascular system. *Am J Cardiol* 2002; 89: 12E–17E.
- [5] Reckelhoff JF. Gender differences in the regulation of blood pressure. *Hypertension* 2001; 37: 1199–1208.
- [6] Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease advantage. *Arch Intern Med* 1995; 155: 57–61.
- [7] Holinka CF, Diczfalusy E, Coelingh Bennink HJ. Estetrol: a unique steroid in human pregnancy. *Climacteric* 2008; 11: S1.
- [8] Knowlton AA, Lee AR. Estrogen and the cardiovascular system. *Pharmacol Ther* 2012; 135: 54–70.
- [9] Taraborrelli S. Physiology, production and action of progesterone. *Acta Obstet Gynecol Scand* 2015; 94: 8–16.
- [10] Iorga A, Cunningham CM, Moazeni S, *et al.* The protective role of estrogen and estrogen receptors in cardiovascular disease and the controversial use of estrogen therapy. *Biol Sex Differ* 2017; 8: 33.
- [11] Nelson LR, Bulun SE. Estrogen production and action. *J Am Acad Dermatol* 2001; 45: S116–S124.
- [12] Garg D, Ng SSM, Baig KM, *et al.* Progesterone-mediated non-classical signaling. *Trends Endocrinol Metab* 2017; 28: 656–668.
- [13] Deng Y, Wang H, Guo X, *et al.* Long-term blood pressure outcomes of laparoscopic adrenalectomy in trHTN patients. *J Transl Int Med* 2021; 11: 275–281.
- [14] GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396: 1223–1249.
- [15] Feldman RD, Limbird LE. GPER (GPR30): a nongenomic receptor (GPCR) for steroid hormones with implications for cardiovascular disease and cancer. *Annu Rev Pharmacol Toxicol* 2017; 57: 567–584.
- [16] Xiong C, Yang B. Revising the hemodynamic criteria for pulmonary hypertension: a perspective from China. *J Transl Int Med* 2023; 11: 1–3.
- [17] Sampson AK, Hilliard LM, Moritz KM, *et al.* The arterial depressor response to chronic low-dose angiotensin II infusion in female rats is estrogen dependent. *Am J Physiol Regul Integr Comp Physiol* 2012; 302: R159–R165.
- [18] Brosnihan KB, Li P, Ganten D, *et al.* Estrogen protects transgenic hypertensive rats by shifting the vasoconstrictor-vasodilator balance of RAS. *Am J Physiol* 1997; 273: R1908–R1915.
- [19] Cherney A, Edgell H, Krukoff TL. NO mediates effects of estrogen on central regulation of blood pressure in restrained, ovariectomized rats. *Am J Physiol Regul Integr Comp Physiol* 2003; 285: R842–R849.
- [20] Ojeda NB, Grigore D, Robertson EB, *et al.* Estrogen protects against increased blood pressure in postpubertal female growth restricted offspring. *Hypertension* 2007; 50: 679–685.
- [21] Brosnihan KB, Senanayake PS, Li P, *et al.* Bi-directional actions of estrogen on the renin-angiotensin system. *Braz J Med Biol Res* 1999; 32: 373–381.
- [22] Mendelsohn ME, Karas RH. The protective effects of estrogen on the cardiovascular system. *N Engl J Med* 1999; 340: 1801–1811.
- [23] Colafella KMM, Denton KM. Sex-specific differences in hypertension and associated cardiovascular disease. *Nat Rev Nephrol* 2018; 14: 185–201.
- [24] Mallareddy M, Hanes V, White WB. Drospirenone, a new progestogen, for postmenopausal women with hypertension. *Drugs Aging* 2007; 24: 453–466.
- [25] Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, *et al.* Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J* 2016; 37: 24–34.
- [26] Pechere-Bertschi A, Burnier M. Gonadal steroids, salt-sensitivity and renal function. *Curr Opin Nephrol Hypertens* 2007; 16: 16–21.
- [27] Tominaga T, Suzuki H, Ogata Y, *et al.* The role of sex hormones and sodium intake in postmenopausal hypertension. *J Hum Hypertens* 1991; 5: 495–500.
- [28] Yanes LL, Romero DG, Iliescu R, *et al.* Postmenopausal hypertension: role of the renin-angiotensin system. *Hypertension* 2010; 56: 359–363.
- [29] Dunne FP, Barry DG, Ferriss JB, *et al.* Changes in blood pressure during the normal menstrual cycle. *Clin Sci (Lond)* 1991; 81: 515–518.
- [30] O’Keeffe LM, Simpkin AJ, Tilling K, *et al.* Sex-specific trajectories of measures of cardiovascular health during ch-



- ildhood and adolescence: a prospective cohort study. *Atherosclerosis* 2018; 278: 190–196.
- [31] Mehta LS, Beckie TM, DeVon HA, *et al.* Acute myocardial infarction in women: a scientific statement from the American Heart Association. *Circulation* 2016; 133: 916–947.
 - [32] Dubey RK, Oparil S, Imthurn B, *et al.* Sex hormones and hypertension. *Cardiovasc Res* 2002; 53: 688–708.
 - [33] Butkevich A, Abraham C, Phillips RA. Hormone replacement therapy and 24-hour blood pressure profile of postmenopausal women. *Am J Hypertens* 2000; 13: 1039–1041.
 - [34] Cacciatore B, Paakkari I, Hasselblatt R, *et al.* Randomized comparison between orally and transdermally administered hormone replacement therapy regimens of long-term effects on 24-hour ambulatory blood pressure in postmenopausal women. *Am J Obstet Gynecol* 2001; 184: 904–909.
 - [35] Szekacs B, Vajo Z, Acs N, *et al.* Hormone replacement therapy reduces mean 24-hour blood pressure and its variability in postmenopausal women with treated hypertension. *Menopause* 2000; 7: 31–35.
 - [36] Crane MG, Harris JJ, Winsor W, 3rd. Hypertension, oral contraceptive agents, and conjugated estrogens. *Ann Intern Med* 1971; 74: 13–21.
 - [37] Notelovitz M. Effect of natural oestrogens on blood pressure and weight in postmenopausal women. *S Afr Med J* 1975; 49: 2251–2254.
 - [38] Utian WH. Effect of postmenopausal estrogen therapy on diastolic blood pressure and bodyweight. *Maturitas* 1978; 1: 3–8.
 - [39] Lip GY, Beevers M, Churchill D, *et al.* Hormone replacement therapy and blood pressure in hypertensive women. *J Hum Hypertens* 1994; 8: 491–494.
 - [40] Pripp U, Hall G, Csemiczky G, *et al.* A randomized trial on effects of hormone therapy on ambulatory blood pressure and lipoprotein levels in women with coronary artery disease. *J Hypertens* 1999; 17: 1379–1386.
 - [41] Schunkert H, Danser AH, Hense HW, *et al.* Effects of estrogen replacement therapy on the renin-angiotensin system in postmenopausal women. *Circulation* 1997; 95: 39–45.
 - [42] Ashraf MS, Vongpatanasin W. Estrogen and hypertension. *Curr Hypertens Rep* 2006; 8: 368–376.
 - [43] Madika AL, MacDonald CJ, Fournier A, *et al.* Menopausal hormone therapy and risk of incident hypertension: role of the route of estrogen administration and progestogens in the E3N cohort. *Menopause* 2021; 28: 1204–1208.
 - [44] Wild RA, Larson JC, Crandall CJ, *et al.* Hormone therapy formulation, dose, route of delivery, and risk of hypertension: findings from the Women’s Health Initiative Observational Study (WHI-OS). *Menopause* 2021; 28: 1108–1116.
 - [45] Ichikawa J, Sumino H, Ichikawa S, *et al.* Different effects of transdermal and oral hormone replacement therapy on the renin-angiotensin system, plasma bradykinin level, and blood pressure of normotensive postmenopausal women. *Am J Hypertens* 2006; 19: 744–749.
 - [46] Akkad AA, Halligan AW, Abrams K, *et al.* Differing responses in blood pressure over 24 hours in normotensive women receiving oral or transdermal estrogen replacement therapy. *Obstet Gynecol* 1997; 89: 97–103.
 - [47] Vongpatanasin W, Tuncel M, Mansour Y, *et al.* Transdermal estrogen replacement therapy decreases sympathetic activity in postmenopausal women. *Circulation* 2001; 103: 2903–2908.
 - [48] Shufelt CL, Merz CN, Prentice RL, *et al.* Hormone therapy dose, formulation, route of delivery, and risk of cardiovascular events in women: findings from the Women’s Health Initiative Observational Study. *Menopause* 2014; 21: 260–266.
 - [49] O’Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. *J Clin Pharmacol* 1995; 35: 18s–24s.
 - [50] Kalenga CZ, Metcalfe A, Robert M, *et al.* Association between the route of administration and formulation of estrogen therapy and hypertension risk in postmenopausal women: a prospective population-based study. *Hypertension* 2023; 80: 1463–1473.
 - [51] Oelkers W, Berger V, Bolik A, *et al.* Dihydrospirorenone, a new progestogen with antimineralocorticoid activity: effects on ovulation, electrolyte excretion, and the renin-aldosterone system in normal women. *J Clin Endocrinol Metab* 1991; 73: 837–842.
 - [52] Oelkers W, Foidart JM, Dombrovicz N, *et al.* Effects of a new oral contraceptive containing an antimineralocorticoid progestogen, drospirenone, on the renin-aldosterone system, body weight, blood pressure, glucose tolerance, and lipid metabolism. *J Clin Endocrinol Metab* 1995; 80: 1816–1821.
 - [53] Pérez-López FR. Clinical experiences with drospirenone: from reproductive to postmenopausal years. *Maturitas* 2008; 60: 78–91.
 - [54] Oelkers W, Helmerhorst FM, Wuttke W, *et al.* Effect of an oral contraceptive containing drospirenone on the renin-angiotensin-aldosterone system in healthy female volunteers. *Gynecol Endocrinol* 2000; 14: 204–213.
 - [55] Palacios S, Foidart JM, Genazzani AR. Advances in hormone replacement therapy with drospirenone, a unique progestogen with aldosterone receptor antagonism. *Maturitas* 2006; 55: 297–307.
 - [56] White WB, Pitt B, Preston RA, *et al.* Antihypertensive effects of drospirenone with 17beta-estradiol, a novel hormone treatment in postmenopausal women with stage 1 hypertension. *Circulation* 2005; 112: 1979–1984.
 - [57] Dogo A, Dožić B, Vujović S, *et al.* Effects of continuous-combined oral drospirenone-estradiol on blood pressure, body weight & lipid profile in early menopausal women. *Indian J Med Res* 2021; 154: 857–865.
 - [58] Zhang GQ, Chen JL, Luo Y, *et al.* Menopausal hormone therapy and women’s health: an umbrella review. *PLoS Med* 2021; 18: e1003731.
 - [59] Rossouw JE, Anderson GL, Prentice RL, *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *JAMA* 2002; 288: 321–333.
 - [60] Anderson GL, Limacher M, Assaf AR, *et al.* Effects of conjugated equine estrogen in postmenopausal women wi-



- th hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701–1712.
- [61] Poon LC, Shennan A, Hyett JA, *et al.* The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. *Int J Gynaecol Obstet* 2019; 146: 390–391.
- [62] Chappell LC, Cluver CA, Kingdom J, *et al.* Pre-eclampsia. *Lancet* 2021; 398: 341–354.
- [63] Bokslag A, van Weissenbruch M, Mol BW, *et al.* Preeclampsia; short and long-term consequences for mother and neonate. *Early Hum Dev* 2016; 102: 47–50.
- [64] Shu C, Han S, Xu P, *et al.* Estrogen and preeclampsia: potential of estrogens as therapeutic agents in preeclampsia. *Drug Des Devel Ther* 2021; 15: 2543–2550.
- [65] Wang XY, Xiong Q, Wang C, *et al.* [Study of estradiol on treatment of preeclampsia in rat model]. *Zhonghua Fu Chan Ke Za Zhi* 2005; 40: 739–742. [In Chinese].
- [66] Lin ZH, Jin J, Shan XY. The effects of estradiol on inflammatory and endothelial dysfunction in rats with preeclampsia. *Int J Mol Med* 2020; 45: 825–835.
- [67] Pei J, Liu Z, Wang C, *et al.* Progesterone attenuates SIRT1-deficiency-mediated pre-eclampsia. *Biomolecules* 2022; 12: 422.
- [68] Liu H, Yu L, Ding Y, *et al.* Progesterone enhances the invasion of trophoblast cells by activating PI3K/AKT signaling pathway to prevent preeclampsia. *Cell Transplant* 2023; 32: 9636897221145682.
- [69] Wan J, Hu Z, Zeng K, *et al.* The reduction in circulating levels of estrogen and progesterone in women with preeclampsia. *Pregnancy Hypertens* 2018; 11: 18–25.
- [70] Zhorzholadze ED, Sanikidze TV, Dzhiikia IV. [The role of hormonal homeostasis in pathogenesis of endothelial dysfunction during preeclampsia]. *Georgian Med News* 2006; 130: 104–107. [In Russian].
- [71] Lan KC, Lai YJ, Cheng HH, *et al.* Levels of sex steroid hormones and their receptors in women with preeclampsia. *Reprod Biol Endocrinol* 2020; 18: 12.
- [72] Ohkuchi A, Ishibashi O, Hirashima C, *et al.* Plasma level of hydroxysteroid (17- β) dehydrogenase 1 in the second trimester is an independent risk factor for predicting preeclampsia after adjusting for the effects of mean blood pressure, bilateral notching and plasma level of soluble fms-like tyrosine kinase 1/placental growth factor ratio. *Hypertens Res* 2012; 35: 1152–1158.
- [73] Berkane N, Liere P, Lefevre G, *et al.* Abnormal steroidogenesis and aromatase activity in preeclampsia. *Placenta* 2018; 69: 40–49.
- [74] Taravati A, Tohidi F, Moniri M, *et al.* Catechol-O-methyltransferase gene polymorphism (Val158Met) and development of pre-eclampsia. *Arch Med Res* 2017; 48: 180–186.
- [75] Wu H, Zhang S, Lin X, *et al.* Pregnancy-related complications and perinatal outcomes following progesterone supplementation before 20 weeks of pregnancy in spontaneously achieved singleton pregnancies: a systematic review and meta-analysis. *Reprod Biol Endocrinol* 2021; 19: 165.
- [76] Milcent C, Dormont B, Durand-Zaleski I, *et al.* Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation* 2007; 115: 833–839.
- [77] Tu JV, Nardi L, Fang J, *et al.* National trends in rates of death and hospital admissions related to acute myocardial infarction, heart failure and stroke, 1994–2004. *CMAJ* 2009; 180: E118–E125.
- [78] Barton M. Cholesterol and atherosclerosis: modulation by oestrogen. *Curr Opin Lipidol* 2013; 24: 214–220.
- [79] Buleishvili M, Lobjanidze N, Ormotsadze G, *et al.* Estrogen related mechanisms of hypertension in menopausal women. *Georgian Med News* 2016; 255: 45–51.
- [80] Inukai T, Takanashi K, Takebayashi K, *et al.* Estrogen markedly increases LDL-receptor activity in hypercholesterolemic patients. *J Med* 2000; 31: 247–261.
- [81] Parini P, Angelin B, Rudling M. Importance of estrogen receptors in hepatic LDL receptor regulation. *Arterioscler Thromb Vasc Biol* 1997; 17: 1800–1805.
- [82] Jones DR, Schmidt RJ, Pickard RT, *et al.* Estrogen receptor-mediated repression of human hepatic lipase gene transcription. *J Lipid Res* 2002; 43: 383–391.
- [83] Persson L, Henriksson P, Westerlund E, *et al.* Endogenous estrogens lower plasma PCSK9 and LDL cholesterol but not Lp(a) or bile acid synthesis in women. *Arterioscler Thromb Vasc Biol* 2012; 32: 810–814.
- [84] Kassi E, Spilioti E, Nasiri-Ansari N, *et al.* Vascular inflammation and atherosclerosis: the role of estrogen receptors. *Curr Med Chem* 2015; 22: 2651–2665.
- [85] de Aloysio D, Gambacciani M, Meschia M, *et al.* The effect of menopause on blood lipid and lipoprotein levels. The Icarus Study Group. *Atherosclerosis* 1999; 147: 147–153.
- [86] Mudali S, Dobs AS, Ding J, *et al.* Endogenous postmenopausal hormones and serum lipids: the atherosclerosis risk in communities study. *J Clin Endocrinol Metab* 2005; 90: 1202–1209.
- [87] Matthews KA, Crawford SL, Chae CU, *et al.* Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol* 2009; 54: 2366–2373.
- [88] Zhou JL, Lin SQ, Shen Y, *et al.* Serum lipid profile changes during the menopausal transition in Chinese women: a community-based cohort study. *Menopause* 2010; 17: 997–1003.
- [89] Erberich LC, Alcântara VM, Picheth G, *et al.* Hormone replacement therapy in postmenopausal women and its effects on plasma lipid levels. *Clin Chem Lab Med* 2002; 40: 446–451.
- [90] Godsland IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974–2000. *Fertil Steril* 2001; 75: 898–915.
- [91] Hulley S, Furberg C, Barrett-Connor E, *et al.* Noncardiovascular disease outcomes during 6.8 years of hormone



- therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002; 288: 58–66.
- [92] Hulley S, Grady D, Bush T, *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998; 280: 605–613.
- [93] Manson JE, Hsia J, Johnson KC, *et al.* Estrogen plus progestin and the risk of coronary heart disease. *N Engl J Med* 2003; 349: 523–534.
- [94] Pérez-López FR, Chedraui P, Gilbert JJ, *et al.* Cardiovascular risk in menopausal women and prevalent related co-morbid conditions: facing the post-Women's Health Initiative era. *Fertil Steril* 2009; 92: 1171–1186.
- [95] Clarkson TB, Meléndez GC, Appt SE. Timing hypothesis for postmenopausal hormone therapy: its origin, current status, and future. *Menopause* 2013; 20: 342–353.
- [96] Galis ZS, Sukhova GK, Lark MW, *et al.* Increased expression of matrix metalloproteinases and matrix degrading activity in vulnerable regions of human atherosclerotic plaques. *J Clin Invest* 1994; 94: 2493–2503.
- [97] Stampfer MJ, Colditz GA, Willett WC, *et al.* Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med* 1991; 325: 756–762.
- [98] Manson JE, Chlebowski RT, Stefanick ML, *et al.* Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA* 2013; 310: 1353–1368.
- [99] Rossouw JE, Prentice RL, Manson JE, *et al.* Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007; 297: 1465–1477.
- [100] Hodis HN, Mack WJ, Henderson VW, *et al.* Vascular effects of early versus late postmenopausal treatment with estradiol. *N Engl J Med* 2016; 374: 1221–1231.
- [101] Baber RJ, Panay N, Fenton A. 2016 IMS recommendations on women's midlife health and menopause hormone therapy. *Climacteric* 2016; 19: 109–150.
- [102] Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure—abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med* 2004; 350: 1953–1959.
- [103] Ceia F, Fonseca C, Mota T, *et al.* Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail* 2002; 4: 531–539.
- [104] Cai A, Qiu W, Xia S, *et al.* Sex-specific characteristics and outcomes in hospitalized heart failure with preserved ejection fraction: the China Cardiovascular Association Database-Heart Failure Center Registry. *Eur Heart J* 2023; 44: 4715–4718.
- [105] Alvarez A, Hermenegildo C, Issekutz AC, *et al.* Estrogens inhibit angiotensin II-induced leukocyte-endothelial cell interactions in vivo via rapid endothelial nitric oxide synthase and cyclooxygenase activation. *Circ Res* 2002; 91: 1142–1150.
- [106] Pedram A, Razandi M, Aitkenhead M, *et al.* Estrogen inhibits cardiomyocyte hypertrophy in vitro. Antagonism of calcineurin-related hypertrophy through induction of MCIP1. *J Biol Chem* 2005; 280: 26339–26348.
- [107] Pedram A, Razandi M, Lubahn D, *et al.* Estrogen inhibits cardiac hypertrophy: role of estrogen receptor-beta to inhibit calcineurin. *Endocrinology* 2008; 149: 3361–3369.
- [108] Clark BA, Elahi D, Epstein FH. The influence of gender, age, and the menstrual cycle on plasma atrial natriuretic peptide. *J Clin Endocrinol Metab* 1990; 70: 349–352.
- [109] Lam CS, Cheng S, Choong K, *et al.* Influence of sex and hormone status on circulating natriuretic peptides. *J Am Coll Cardiol* 2011; 58: 618–626.
- [110] Karjalainen AH, Ruskoaho H, Vuolteenaho O, *et al.* Effects of estrogen replacement therapy on natriuretic peptides and blood pressure. *Maturitas* 2004; 47: 201–208.
- [111] Solomon SD, McMurray JJV, Anand IS, *et al.* Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; 381: 1609–1620.
- [112] Petrov G, Regitz-Zagrosek V, Lehmkuhl E, *et al.* Regression of myocardial hypertrophy after aortic valve replacement: faster in women? *Circulation* 2010; 122: S23–S28.
- [113] Dworatzek E, Mahmoodzadeh S, Schriever C, *et al.* Sex-specific regulation of collagen I and III expression by 17 β -estradiol in cardiac fibroblasts: role of estrogen receptors. *Cardiovasc Res* 2019; 115: 315–327.
- [114] Martos R, Baugh J, Ledwidge M, *et al.* Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. *Circulation* 2007; 115: 888–895.
- [115] Dworatzek E, Baczko I, Kararigas G. Effects of aging on cardiac extracellular matrix in men and women. *Proteomics Clin Appl* 2016; 10: 84–91.
- [116] Doshi SB, Agarwal A. The role of oxidative stress in menopause. *J Midlife Health* 2013; 4: 140–146.
- [117] Silberman GA, Fan TH, Liu H, *et al.* Uncoupled cardiac nitric oxide synthase mediates diastolic dysfunction. *Circulation* 2010; 121: 519–528.
- [118] Majmudar NG, Robson SC, Ford GA. Effects of the menopause, gender, and estrogen replacement therapy on vascular nitric oxide activity. *J Clin Endocrinol Metab* 2000; 85: 1577–1583.
- [119] Sabbatini AR, Kararigas G. Menopause-related estrogen decrease and the pathogenesis of HFpEF: JACC review topic of the week. *J Am Coll Cardiol* 2020; 75: 1074–1082.
- [120] Redfield MM, Jacobsen SJ, Borlaug BA, *et al.* Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation* 2005; 112: 2254–2262.
- [121] Gökçe M, Karahan B, Erdöl C, *et al.* Left ventricular diastolic function assessment by tissue Doppler echocardiography in relation to hormonal replacement therapy in postmenopausal women with diastolic dysfunction. *Am J Ther* 2003; 10: 104–111.
- [122] Voutilainen S, Hippeläinen M, Hulkko S, *et al.* Left ventricular diastolic function by Doppler echocardiography in relation to hormonal replacement therapy in healthy postmenopausal women. *Am J Cardiol* 1993; 71: 614–617.
- [123] Lim WK, Wren B, Jepson N, *et al.* Effect of hormone re-



- placement therapy on left ventricular hypertrophy. *Am J Cardiol* 1999; 83: 1132–1134, a1139.
- [124] Light KC, Hinderliter AL, West SG, *et al.* Hormone replacement improves hemodynamic profile and left ventricular geometry in hypertensive and normotensive postmenopausal women. *J Hypertens* 2001; 19: 269–278.
- [125] Sophonsritsuk A, Appt SE, Clarkson TB, *et al.* Differential effects of estradiol on carotid artery inflammation when administered early versus late after surgical menopause. *Menopause* 2013; 20: 540–547.
- [126] Michalson KT, Groban L, Howard TD, *et al.* Estradiol treatment initiated early after ovariectomy regulates myocardial gene expression and inhibits diastolic dysfunction in female cynomolgus monkeys: potential roles for calcium homeostasis and extracellular matrix remodeling. *J Am Heart Assoc* 2018; 7: e009769.
- [127] Poorthuis MHF, Yao P, Chen Y, *et al.* Risks of stroke and heart disease following hysterectomy and oophorectomy in Chinese premenopausal women. *Stroke* 2022; 53: 3064–3071.
- [128] Ley SH, Li Y, Tobias DK, *et al.* Duration of reproductive life span, age at menarche, and age at menopause are associated with risk of cardiovascular disease in women. *J Am Heart Assoc* 2017; 6: e006713.
- [129] Honigberg MC, Zekavat SM, Aragam K, *et al.* Association of premature natural and surgical menopause with incident cardiovascular disease. *JAMA* 2019; 322: 2411–2421.
- [130] Price MA, Alvarado BE, Rosendaal NTA, *et al.* Early and surgical menopause associated with higher Framingham Risk Scores for cardiovascular disease in the Canadian Longitudinal Study on Aging. *Menopause* 2021; 28: 484–490.
- [131] Stuenkel CA, Davis SR, Gompel A, *et al.* Treatment of symptoms of the menopause: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2015; 100: 3975–4011.
- [132] Lumsden MA, Davies M, Sarri G. Diagnosis and management of menopause: the National Institute of Health and Care Excellence (NICE) Guideline. *JAMA Intern Med* 2016; 176: 1205–1206.
- [133] Nappi RE. The 2022 hormone therapy position statement of the North American Menopause Society: no news is good news. *Lancet Diabetes Endocrinol* 2022; 10: 832–834.
- [134] Stuenkel CA, Gompel A, Davis SR, *et al.* Approach to the patient with new-onset secondary amenorrhea: is this primary ovarian insufficiency? *J Clin Endocrinol Metab* 2022; 107: 825–835.
- [135] Stuenkel CA, Gompel A. Primary ovarian insufficiency. *N Engl J Med* 2023; 388: 154–163.
- [136] Lakshman R, Forouhi NG, Sharp SJ, *et al.* Early age at menarche associated with cardiovascular disease and mortality. *J Clin Endocrinol Metab* 2009; 94: 4953–4960.
- [137] Bubach S, De Mola CL, Hardy R, *et al.* Early menarche and blood pressure in adulthood: systematic review and meta-analysis. *J Public Health (Oxf)* 2018; 40: 476–484.
- [138] Peters SA, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. *Heart* 2018; 104: 1069–1075.
- [139] Canoy D, Beral V, Balkwill A, *et al.* Age at menarche and risk of coronary heart and other vascular diseases in a large UK cohort. *Circulation* 2015; 131: 237–244.
- [140] Zhu D, Chung HF, Dobson AJ, *et al.* Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health* 2019; 4: e553–e564.
- [141] Roach RE, Helmerhorst FM, Lijfering WM, *et al.* Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev* 2015; 2015: Cd0111054.
- [142] Jick H, Jick S, Myers MW, *et al.* Risk of acute myocardial infarction and low-dose combined oral contraceptive. *Lancet* 1996; 347: 627–628.
- [143] Ge SQ, Tao X, Cai LS, *et al.* Associations of hormonal contraceptives and infertility medications on the risk of venous thromboembolism, ischemic stroke, and cardiovascular disease in women. *J Investig Med* 2019; 67: 729–735.
- [144] Weill A, Dalichampt M, Raguideau F, *et al.* Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ* 2016; 353: i2002.
- [145] Hannaford PC, Iversen L, Macfarlane TV, *et al.* Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. *BMJ* 2010; 340: c927.
- [146] Vessey M, Yeates D, Flynn S. Factors affecting mortality in a large cohort study with special reference to oral contraceptive use. *Contraception* 2010; 82: 221–229.
- [147] Lidegaard Ø, Løkkegaard E, Jensen A, *et al.* Thrombotic stroke and myocardial infarction with hormonal contraception. *N Engl J Med* 2012; 366: 2257–2266.
- [148] Johansson T, Fowler P, Ek WE, *et al.* Oral contraceptives, hormone replacement therapy, and stroke risk. *Stroke* 2022; 53: 3107–3115.
- [149] Dou W, Huang Y, Liu X, *et al.* Associations of oral contraceptive use with cardiovascular disease and all-cause death: evidence from the UK Biobank cohort study. *J Am Heart Assoc* 2023; 12: e030105.
- [150] Hayes SN, Tweet MS, Adlam D, *et al.* Spontaneous coronary artery dissection: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; 76: 961–984.
- [151] Kim ESH. Spontaneous coronary artery dissection. *N Engl J Med* 2020; 383: 2358–2370.
- [152] Tschiderer L, Seekircher L, Kunutsor SK, *et al.* Breastfeeding is associated with a reduced maternal cardiovascular risk: systematic review and meta-analysis involving data from 8 studies and 1,192,700 parous women. *J Am Heart Assoc* 2022; 11: e022746.
- [153] WHO Guidelines Approved by the Guidelines Review Committee. Infant and Young Child Feeding: Model Chapter for Textbooks for Medical Students and Allied Health Professionals. Geneva; World Health Organization Copyright© 2009, World Health Organization 2009.
- [154] Gutkowska J, Jankowski M. Oxytocin revisited: its role in cardiovascular regulation. *J Neuroendocrinol* 2012; 24: 599–608.
- [155] Reiss AB, Glass DS, Lam E, *et al.* Oxytocin: potential to



- [156] mitigate cardiovascular risk. *Peptides* 2019; 117: 170089.
Parikh NI, Gonzalez JM, Anderson CAM, *et al.* Adverse pregnancy outcomes and cardiovascular disease risk: un-

ique opportunities for cardiovascular disease prevention in women: a scientific statement from the American Heart Association. *Circulation* 2021; 143: e902–e916.

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