Sex Hormones and Cardiovascular Disease in Relation to Menopause

Catherine Kim, MD, MPH[a,b,c,*], Melissa Wellons, MD, MHS[d]

KEYWORDS

• Menopause • Estradiol • Hypertension • Glucose • Lipids • Cholesterol
• Epidemiology • Management

KEY POINTS

- Early menopause and bilateral oophorectomy predict the increased risk of cardiovascular disease, although whether this risk is mediated via changes in sex hormones or shared genetic and environmental precursors is not established.
- Changes in cardiovascular risk factors during the menopausal transition reflect chronologic as well as reproductive aging and thus tend to be incremental rather than drastic.
- Although endogenous estradiol may decline sharply during menopause, exogenous estradiol therapy has not been demonstrated to lower incidence of cardiovascular events.

INTRODUCTION

Natural menopause is defined as the cessation of menstruation among women who have not undergone hysterectomy or bilateral oophorectomy. The cessation of menstruation results from depletion of the functional ovarian follicle pool, which is commonly believed to be fixed at birth.[1] With the depletion of this pool, the ovaries decrease the production of estradiol (E2), and the pituitary increases production of follicle-stimulating hormone (FSH).[2] The term "perimenopause" is often loosely applied to the several years flanking the final menstrual period (FMP) but technically is defined by menstrual irregularity according to the international Stages of Reproductive Aging Workshop (STRAW) consortium.[3] According to STRAW criteria, women begin perimenopause when their menses vary by $\geq$ 7 days between consecutive cycles.[3] Women are then classified as postmenopausal when a year has passed without a menstrual period. Women who have cessation of menses due to hysterectomy or bilateral oophorectomy cannot be staged according to STRAW criteria.

[a] Department of Medicine, University of Michigan, Ann Arbor, MI, USA; [b] Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI, USA; [c] Department of Epidemiology, University of Michigan, Ann Arbor, MI, USA; [d] Department of Medicine, Vanderbilt University Medical Center, 3841 Green Hills Village Dr #200, Nashville, TN 37215, USA
* Corresponding author. 2800 Plymouth Road, Building 16, Room 405E, Ann Arbor, MI.
E-mail address: cathkim@umich.edu

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Humans and several whale species are among the few species that undergo cessation of menses years before death.[4] Thus, menopause represents a milestone of aging that is unique to humans and also universal for women. In this review, the authors outline how this milestone relates to cardiovascular disease (CVD) risk. Specifically, the authors discuss shared antecedents of menopause and cardiovascular disease as well as the changes in sex hormone levels and CVD risk factors during the menopausal transition. The authors also review the trials of exogenous estrogen for modification of CVD risk and current guidelines for the use of such therapies in these populations.

DETERMINANTS OF MENOPAUSE

It is unclear whether menopause is a product of the same aging processes that affect aging generally or has an independent impact on diseases of aging (**Fig. 1**). Intriguingly, the polymorphisms that predict age at natural menopause involve steroid hormone metabolism and biosynthesis pathways[5] as well as variants that slow aging,[6] suggesting that the hormonal changes of menopause may be driven by the same underlying process involved in aging of other organ systems.

Age at natural menopause, used interchangeably with age at the FMP, occurs at approximately 50 years of age. However, there is significant variation by country, geography within countries, racial/ethnic group, and health status.[7] As opposed to women in North America and northern Europe, women living other regions of the world including Latin America,[8] India,[9] Singapore,[10] China,[9] and Korea[11] have slightly younger ages of menopause. Within the United States, women who lived in the southern United States reported an age at FMP which was 10.8 months earlier than women

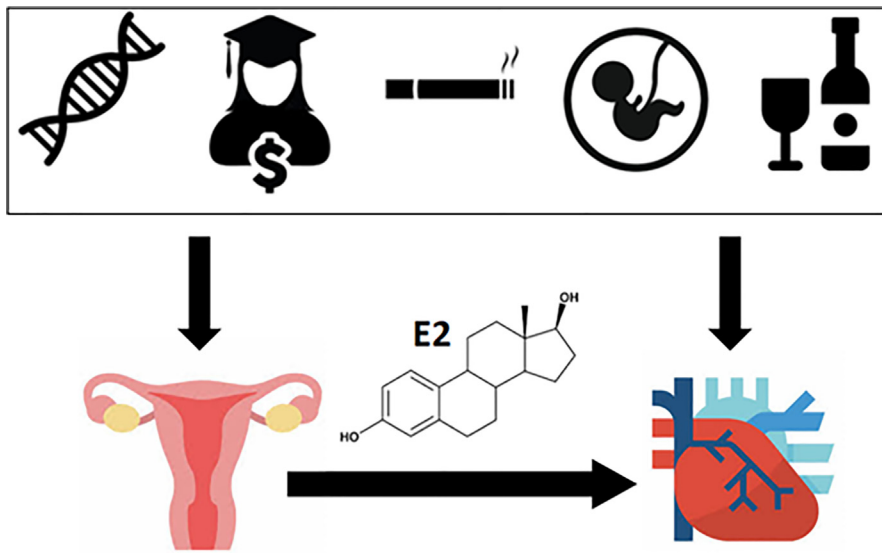

Fig. 1. Conceptual model of the relationship between menopause and cardiovascular disease. Age at menopause and cardiovascular disease share risk factors, including (from *left*) generic polymorphisms, socioeconomic position, cigarette use, intrauterine environment, and alcohol use. The extent to which these factors and hormonal changes that characterize the menopausal transition have independent effects from aging on cardiovascular disease risk is not known.

who lived in the northeast; 8.4 months earlier than women who lived in the midwest; and 6 months earlier than women who lived in the west[12] even after consideration of race/ethnicity and other socioeconomic factors. Cohort studies have noted that Latinas in the United States have younger age of menopause compared with non-Latino whites, who in turn have younger ages of menopause than Japanese-Americans.[13,14] Some of these differences may be explained by familial concordance[15] as well as modifiable factors including higher socioeconomic position,[16] birth weight that is neither small nor large for gestational age,[17] lack of cigarette use, and increased alcohol consumption which are associated with older age of menopause, with possible roles for body mass index (BMI), exercise, and dietary quality.[7,13,18–20] Of note, these are also protective risk factors for CVD disease.

AGE AT MENOPAUSE AND CARDIOVASCULAR RISK

Whether through shared antecedents or characteristic changes in the hormonal milieu, it has been consistently demonstrated that age at menopause predicts comorbidities in later life, particularly CVD comorbidity. Although women have lower risk of acute coronary disease death than men, the degree of protection decreases with age.[21] Younger age at FMP, particularly when classified as less than 40 years of age (premature menopause) or between 40 and 45 years of age (early menopause), consistently predicts higher risk of CVD risk score,[22] CVD events,[23] and mortality compared with older age at FMP.[24–28] In a pooled analysis of data from several cohorts, including the Atherosclerosis Risk in Communities Study, the Multi-Ethnic Study of Atherosclerosis, and the Jackson Heart Study, early menopause was associated with greater risk of incident coronary heart disease, stroke, and heart failure.[26] This risk was more pronounced among women with type 2 diabetes. Antihypertensive medication, lipid-lowering medication, and estrogen therapy were taken into account, suggesting that the greater risk observed in women with early menopause may require novel interventions other than standard risk factor modification.[26] Other cohort studies have reported similar associations between younger age at menopause and increased CVD risk[27,28] Of note, despite significant associations between early menopause and CVD risk, there is no incremental benefit in risk prediction in addition to traditional risk factors, suggesting that the detrimental effects are largely mediated through adverse levels of these risk factors.[29]

Women who undergo hysterectomy or bilateral oophorectomy before natural cessation of menses tend to have poorer CVD risk profiles than women who do not.[30–32] When these profiles are considered, hysterectomy seems to have a limited impact on risk of CVD events. In contrast, bilateral oophorectomy performed more than 5 years before natural menopause seems to have a larger effect on CVD events and mortality.[33,34] One pooled analysis noted that CVD risk was most pronounced in women who underwent surgical menopause at younger ages, particularly at less than 40 years of age, compared with women who experienced natural menopause between 50 and 54 years of age.[27] Presumably, this is due to the declines in hormone levels that are observed with oophorectomy as compared with hysterectomy. However, it is possible that women who underwent oophorectomy had greater risk due to unspecified factors relating to the indications for more extensive surgery as opposed to women who underwent hysterectomy only.

SEX HORMONE CHANGES DURING MENOPAUSE

Women who undergo natural menopause experience declines in E2 and increases in FSH during the transition.[35] The Study of Women's Health Across the Nation (SWAN)

is a multiracial cohort study that noted that these hormonal changes may vary in speed (Fig. 2).[35] Several trajectories of hormone changes were identified among women who did not undergo gynecologic surgery.[35,36] Approximately one-third of women experienced a slight increase in E2 before the FMP, followed by steep declines, whereas about one-fourth of women experienced more gradual declines in E2. These trajectories were mirrored by trajectories in FSH, where some women experienced sharp increases in FSH, whereas others experienced more gradual increases. Obese women were more likely to have gradual changes in hormone levels.[35]Although other sex steroids also change during the menopausal transition, the fluctuation in levels is generally less dramatic than that observed with E2 and FSH.[37,38] Androgen levels, including testosterone (T), androstenedione (A4), and dehydroepiandrosterone sulfate (DHEAS), are relatively stable as compared with E2 during the natural menopause transition. With the marked decline in ovarian E2 production after the FMP, the adrenal gland becomes a particularly important source of sex steroids, particularly DHEAS, which can be aromatized to A4, which in turn is converted to estrone (E1), the predominant circulating estrogen after the FMP. DHEAS modestly increases in the perimenopause, with constant levels of T and minimal declines in A4, regardless of BMI (Fig. 3).[39] The resulting postmenopausal hormonal milieu is more androgenic than the premenopausal milieu.

Not surprisingly, women who undergo oophorectomy have lower total and unbound E2 and T postoperatively compared with preoperative levels,[40] consistent with the fact that the ovaries are an important source of T as well as E2 production. The postsurgical milieu is characterized by lower absolute androgen levels due to the loss of T from the ovary,[41–43] although the environment is predominantly androgenic due to the loss of E2 production and continued androgen production by the adrenal glands.

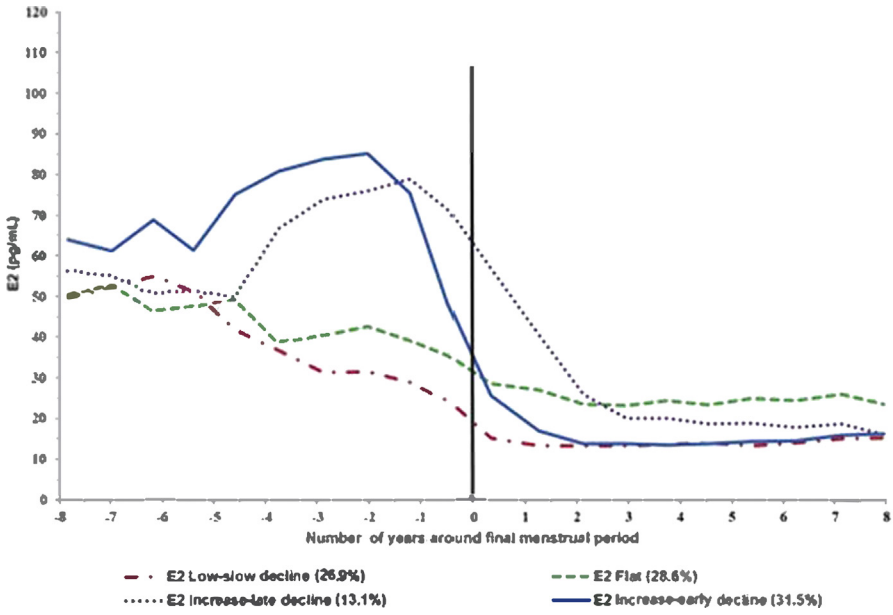

Fig. 2. Trajectories of estradiol (E2) in the Study of Women's Health Across the Nation (SWAN). Reprinted with permission from the American College of Obstetricians and Gynecologists, Obstetrics and Gynecology, 2018;45(4):641-661. With permission from the Foreign Policy Research Institute.

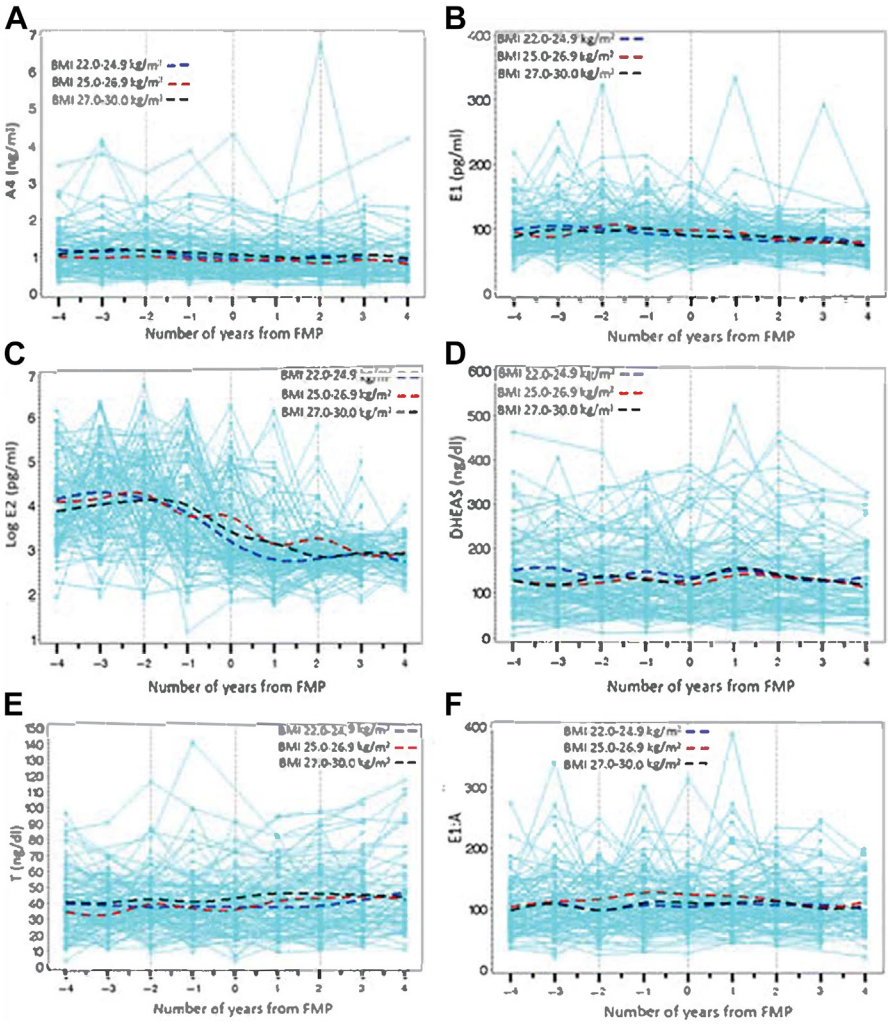

Fig. 3. Changes in sex steroid levels during the menopausal transition. "0" indicates the year of the final menstrual period (FMP); "1" indicates 1 year after the FMP, and "-1" indicates 1 year before the FMP. Panel (*A*) Androstenedione. (*B*) Estrone. (*C*) Log Estradiol. (*D*) Dehydroepiandrosterone-sulfate. (*E*) Testosterone. (*F*) Ratio of estrone: androstenedione. (*From* Kim C, Harlow SD, Zheng H, McConnell DS, Randolph JF Jr. Changes in androstenedione, dehydroepiandrosterone, testosterone, estradiol, and estrone over the menopausal transition. Womens Midlife Health. 2017;3:9.)

CHANGES IN CARDIOVASCULAR RISK FACTORS DURING MENOPAUSE AND CARDIOVASCULAR RISK AFTER MENOPAUSE

What implications do these hormone changes have for CVD risk factor levels in aging women? Despite anecdotal observations of weight gain during menopause, much of weight gain is associated with chronologic aging as opposed to menopause stage.[44] Although sex hormone changes correlate with future increases in waist circumference in vice versa, waist circumference predicts future E2 levels to a greater extent than

vice versa.[45] SWAN conducted annual assessments of levels of CVD risk factors during the menopausal transition. Low-density lipoprotein cholesterol (LDL-C) increases precipitously,[46] mirroring the declines in E2 (**Fig. 4**). However, increases in blood pressure and insulin increased linearly rather than sharply; glucose levels did not increase.[46] These patterns suggest that the increased CVD risk observed in midlife women may be due to concurrent chronologic aging as well as changes in sex hormone profile. This profile is not only based on E2 changes; adverse profiles of CVD risk factors are associated with indicators of increased androgenicity, namely lower sex hormone-binding globulin and higher free androgen index.[47]

Whether the relatively rapid changes in lipid profile and the more gradual changes in other risk factors translate to marked increases in CVD risk are uncertain. The burden of coronary artery calcification (CAC) and carotid intima media thickness is generally too low to assess perimenopausal progression during this phase of life. Arterial stiffness seems to increase markedly beginning the year before and ending the year after transition, suggesting that at least this marker may be sensitive to the menopausal transition.[48]

Poor sleep is commonly attributed to menopause. Sleep disorders, especially sleep apnea, have emerged as contributors to arterial stiffening and diagnosed hypertension. Recent analyses of the longitudinal SWAN and Penn Ovarian Aging studies have found that, for the majority of women, sleep complaints remain surprisingly stable over the course of the menopausal transition, with premenopausal sleep complaints predicting postmenopausal sleep complaints in the majority of women.[49–51] In a minority of women, roughly 15%, sleep worsens over the menopausal transition as marked by a significant increase in overnight awakenings.

Menopausal vasomotor symptoms (VMS) are associated with bothersome awakenings. Menopause may also contribute to other physiologic mechanisms that disrupt sleep. For example, a cross-sectional study of 219 women from the Wisconsin Sleep Cohort Study, the Sleep in Midlife Women Study, found that perimenopausal and postmenopausal women had significantly higher apnea–hypopnea indices as compared with premenopausal women (21% and 31% higher, respectively)[52] Analysis of the Nurses Health Study revealed a higher incidence of obstructive sleep apnea

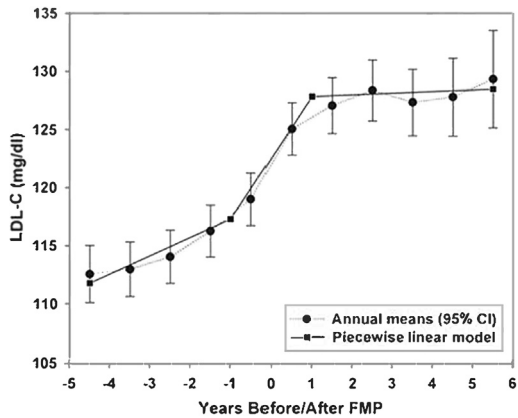

Fig. 4. Increases in low-density lipoprotein cholesterol (LDL-C) during the menopausal transition. (*From* Matthews KA, Crawford SL, Chae CU, et al. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition?. J Am Coll Cardiol. 2009;54(25):2366-2373.)

(OSA) among women with early menopause versus later menopause and in women with surgical menopause versus natural menopause.[53] The researchers concluded that this finding supports a role for menopausal hormonal changes, particularly abrupt ones, in the pathogenesis of OSA.

IMPACT OF EXOGENOUS ESTROGEN ON CARDIOVASCULAR DISEASE

The observation that estrogen therapy might mitigate the increased risk of CVD events among women who had undergone bilateral oophorectomy dates back to at least 1987.[54] Interestingly, this early report from the first cohort of the Nurses' Health Study also noted that estrogens did not mitigate the risk of CVD events in women who had undergone natural menopause compared with women in premenopause, a finding that would predict the general minimal impact that estrogen therapy has had on CVD outcomes among women randomized to estrogen use in subsequent trials.

Once widely used for chronic disease prevention, estrogen therapy is currently used for relief of symptoms[55] including VMS or the genitourinary syndrome of menopause, which includes vaginal dysesthesias, dyspareunia, and urinary symptoms. The Women's Health Initiative (WHI) was a large United States randomized trial of estrogen therapy (with and without progestin) among women who averaged approximately 63 years of age at randomization. Women who had undergone a hysterectomy were assigned to conjugated equine estrogen alone (n = 5310) versus placebo (n = 5429), whereas women with an intact uterus were assigned to conjugated equine estrogen plus medroxyprogesterone (n = 8506) versus placebo (n = 8102).[56] Neither estrogen therapy alone nor estrogen plus progestin therapy seemed to decrease the risk of coronary and risk of stroke was increased.[56] After the study results were released in 2001, prescription of estrogen-based therapies declined precipitously and remains low.[57] In the meantime, a 2017 systematic review examined long-term risks associated with estrogen therapy, including follow-up from the WHI.[58] Although risk of myocardial infarction gradually declined over time, risk of stroke remained elevated over a decade after randomization.[58]

The observation that there was suggestion of benefit in younger women aged 50 to 59 years led to the timing hypothesis, which states that estrogen therapy may be of greater benefit if initiated closer to the time of menopause.[59] Of note, this trend did not reach statistical significance, although the WHI was not powered to conduct stratified analyses by age. Three randomized studies have examined whether randomization to E2 use might slow progression of atherosclerosis among women who underwent menopause within the past 5 years. A subanalysis of the WHI that examined CAC as an outcome reported that among women aged 50 to 59 years at enrollment, CAC burden at trial completion was lower in women assigned to estrogen than placebo.[60] Women in the ELITE (Early vs Late Intervention Trial with Estradiol) trial were randomized to oral 17-beta-E2 (and progesterone if they had a uterus) or placebo.[61] Carotid artery intima-media thickness (CIMT) was assessed every 6 months, and CAC was assessed at study end. CAC levels did not vary by randomization assignment. Among women who were 10 or more years postmenopause at the time of randomization, the rates of CIMT progression were similar by randomization arm. Among women who were less than 6 years postmenopause at randomization, CIMT increased more slowly among women randomized to E2 (0.0078 mm per year in placebo vs 0.0044 mm per year in the E2 group, P = 0.008). The degree of progression was inversely associated with plasma E2 level.[62] In contrast, another randomized trial, Kronos Early Estrogen Prevention Study, assigned recently postmenopausal women (between 6 and 36 months from their last period) to approximately 48 months of

conjugated equine estrogen, transdermal 17 beta-E2, or placebo. The progression of CIMT did not vary by treatment group (31.9 vs 35.1 vs 33 μm, $P = 0.82$),[63] and the progression of CAC did not vary by treatment group.[64,65] Follow-up of both cohorts continue with examination of other intermediate markers (such as pericardial fat) to determine whether an impact on outcomes will be observed.

Even as a favorable impact on markers of atherosclerosis is not proven, estrogen therapy seems to minimally increase CVD risk when initiated within the decade after menopause and when used in women without preexisting CVD and other contraindications.[58,66] In particular, transdermal E2 at low doses (<50 mcg/day) combined with micronized progesterone was not associated with either thrombotic events nor stroke risk in meta-analyses of trials and observational studies, although safety compared with oral E2 is not proven.[66] A Danish study examined the impact of randomization to E2 therapy versus no therapy and found a lower risk of a composite outcome of death, hospital admission for heart failure, and myocardial infarction.[32] However, this trial has been criticized for the lack of a placebo as well as the use of an outcome that was not prespecified.[67] Overall, in postmenopausal women generally, combined continuous estrogen and progesterone therapy increases rather than decreases the risk of coronary events although on a magnitude of several cases per thousand users, as well as thromboembolic events, breast cancer, dementia, and gallbladder disease.[58,66] Thus, the use of such therapy for preventive purposes is limited. These recommendations are similar for women who undergo hysterectomy and/or oophorectomy; among the women who experience surgical menopause in the WHI, estrogen therapy did not impact CVD events, although women aged 50 to 59 years seemed to derive some mortality benefit.[68]

IMPACT OF EXOGENOUS ANDROGENS ON CARDIOVASCULAR DISEASE

Recently, the Endocrine Society drafted guidance on the use of T therapy in women.[69] Included in the guidance are statements on the relationship between T therapy and cardiovascular health. Noted is that oral T therapy worsens lipid profiles, raising LDL-C and lowering high-density lipoprotein cholesterol. In contrast, non-oral T therapies, when given at doses approximating premenopausal T levels, are not associated with a worsening of lipid profiles nor did they seem to negatively affect blood pressure or glucose metabolism. In combined data from 9 studies, deep venous thromboses are four-fold more common in women randomized to T; however, this finding is not statistically significant. Myocardial infarction, stroke, and cardiovascular death are no more common in women receiving T. Overall, CVD event rates are low in the existing studies of T therapy, reflecting study designs that have likely excluded women at high risk of CVD.[70] Of note, polycystic ovary syndrome is characterized by high endogenous T levels and is not associated with lower risk of CVD.[71]

ESTROGEN THERAPY IN POSTMENOPAUSAL WOMEN

Estrogen therapy can mitigate menopausal hot flashes or the genitourinary syndrome of menopause which includes vaginal itching, dryness, dyspareunia, and urinary symptoms. Contraindications to estrogen therapy include breast cancer, gallbladder disease, hypertriglyceridemia, and history of thrombosis as well as history of CVD or elevated risk of CVD. Several CVD risk calculators, including the commonly used prospective diabetes study (UKPDS) engine[72] and the Pooled Cohort Equations risk engine[73] can be used to calculate CVD risk in women. Despite variations in the weighting of particular factors, the classification of persons at medium versus high risk is fairly consistent across calculators. Women with high risk of CVD events due to suboptimal levels of risk factors, family history, or age should not receive estrogen therapy. Usually, this

includes women with who are older than 60 years of age, more than 10 years from their last menses, and have abnormal risk factor levels.[74] Women with significantly elevated risk of breast cancer because of unfavorable family or reproductive histories should not receive estrogen therapy, and women considering estrogen therapy should also be willing to engage in mammographic imaging and routine follow-up.

If women and their clinicians at low risk for CVD events and breast cancer choose to initiate estrogen therapy, transdermal or oral estrogen therapy can be initiated. E2, specifically 17-beta-E2, may offer hypothetical benefit over conjugated equine estrogen as estradiol is released by the ovary, whereas conjugated equine estrogen is not identical. Transdermal E2 is generally preferred, as oral E2 may adversely affect inflammation and coagulation profiles [75] and thromboembolic risk to a greater extent than transdermal E2.[55] If oral E2 is initiated, 10-year CVD risk should be low, and oral E2 should be avoided in women at moderate or high risk.[76] In general, the lowest dose for relief of symptoms should be given, along with progesterone to reduce the risk of uterine cancer in women who have a uterus. Transdermal forms include E2 only patches (applied once or twice weekly, at E2 doses ranging from 0.025 to 0.14 mg per day), E2–progestin patches (applied once or twice weekly), gels (ranging from 0.25 to 0.75 mg per applicator), intravaginal creams (0.1 mg E2 per gram or Premarin given daily), and vaginal suppositories (10 mcg per tablet, usually inserted twice a week). Rings are available both in higher dose formulations for hot flash relief (ranging from 0.05 to 0.1 mg per day over 3 months) to formulations targeting genitourinary syndromes of menopause (7.5 mcg per day over 3 months). Oral E2 forms range from 0.5 mg per day to 2 mg per day, and oral E2–progestin formulations are also available for women who have uteruses.

Such therapy is usually tapered after 4 to 5 years of use, due to the observation in the WHI that breast cancer risk increased after 5 years of use. However, due to the duration of hot flashes, women may opt to continue therapy with repeated efforts at gradual tapers over a period of 6 months or even longer. Although about one-quarter of women have relatively mild hot flashes or VMS that subside several years after the FMP, approximately another quarter have persistent VMS even a decade after the FMP (**Fig. 5**).[77] Although estrogen therapy is typically not recommended for women over the age of 60 years, the figure suggests that estrogen therapy could potentially is of use in this subpopulation at younger ages. Women were more likely to have persistent VMS if they had greater alcohol intake, higher depressive and anxiety symptoms, and poorer health status.[77]

Among women who experience menopause at younger ages, particular before the age of 40 years, estrogen therapy is usually prescribed primarily for preservation of bone health or cardiovascular health.[78] Although randomized trial data are currently lacking, there are currently studies underway to detect benefit.[79] In the meantime, 17-beta-E2 (and progesterone, if women retain their uteruses) is usually given at higher doses than in older women. Combined estrogen–progestin contraceptive pills provide higher doses of E2 than the doses of E2 typically given among older perimenopausal women. Oral contraceptive pills have the added benefit of providing contraception should ovarian activity resume. Such therapy is typically continued until the age of 50 years, although the length of use is primarily based on average at the FMP rather than trials examining length of use.

TESTOSTERONE THERAPY IN POSTMENOPAUSAL WOMEN

Hyposexual desire disorder is the sole evidence-based indication for T therapy in postmenopausal women, although it is not an Food and Drug Administraiton (FDA)

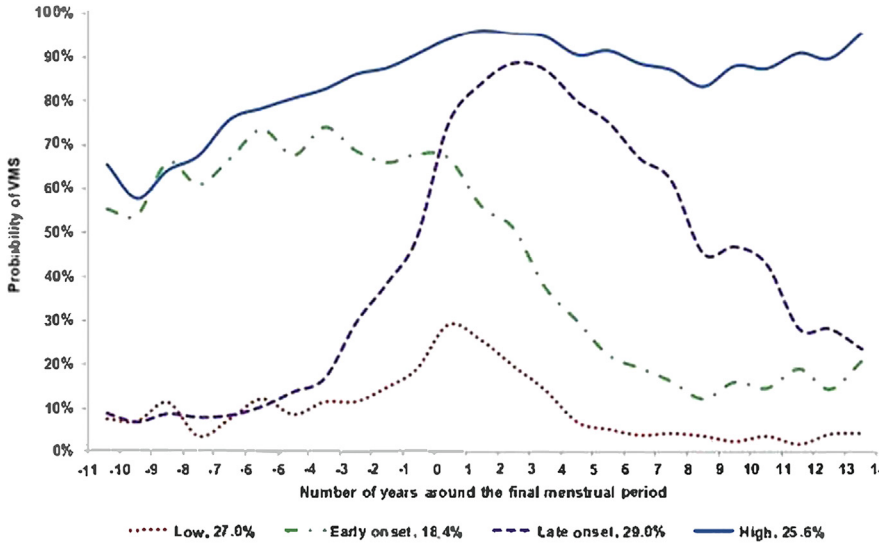

Fig. 5. Trajectories of vasomotor symptoms (VMS) in the Study of Women's Health Across the Nation (SWAN). Reprinted with permission from the American College of Obstetricians and Gynecologists, Obstetrics and Gynecology, 2018;45(4):641-661. With permission from the Foreign Policy Research Institute.

approved therapy. The ability of clinicians to balance this benefit against long-term chronic disease risk is limited by the lack of long-term randomized studies. In addition, for postmenopausal women who desire supplemental T, no FDA-approved T preparation exists that is formulated to restore premenopausal T levels. Although oral estrogen and T containing products exist in the marketplace (eg, esterified estrogens and methyltestosterone containing tablets), the known negative effects of oral T on lipid metabolism limit enthusiasm for its use. Off-label use of male T preparations may be considered with the caveat that there is minimal evidence on the effect of these preparations on women's cardiovascular health.[69] Currently, there are no biochemical criteria for what constitutes low androgens in women (regardless of menopausal state), but levels of total T greater than 2.8 nmol/L (70 ng/dL) should raise concerns about pathological processes.

Data regarding postmenopausal supplementation of other androgen formulations, particularly DHEA, are even more sparse than for T. In 2014, the Endocrine Society recommended against the use of DHEA for women with low androgen levels as are commonly found in adrenal insufficiency, surgical menopause, hypopituitarism, or other conditions due to the lack of data noting improved symptoms or signs with therapy as well as the lack of long-term data on risk.[80] Other medical professional societies such as the North American Menopause Society have also recommended against the routine use of DHEA, with the exception of vaginal formulations for genitourinary symptoms. This 2022 position has been endorsed by an international consortium of menopause societies.[76]

SUMMARY

The implications of menopause management are particularly important with the aging of the population and increasing awareness of the importance of midlife risk on

longevity. Our understanding of the relationships between reproductive milestones and CVD continues to evolve particularly regarding shared determinants of health. The life course approaches that examine in utero, childhood, and early adult exposures on milestones such as menopause and CVD risk are needed to better understand when to intervene and which risk factors need to be targeted to improve downstream determinants of health.

In the interim, clinicians should engage in shared decision-making regarding the use of estrogen therapies for mitigation of menopausal symptoms. Low-dose oral or transdermal formulations can improve quality of life and are safe among the majority of women who undergo surgical menopause or natural menopause.

CLINICS CARE POINTS

- For management of menopausal symptoms, particularly hot flashes and vaginal discomfort, transdermal estradiol formulations may have lower risk than oral formulations. Limiting length of use may limit risk of breast cancer.
- Management of cardiovascular risk during menopause focuses on optimization of weight and cardiovascular risk factors, particularly tobacco use, blood pressure, and cholesterol. Aggressive management of these profiles in midlife likely benefits other long-term outcomes, including cognition.
- Exogenous estradiol should not be used solely to reduce risk of cardiovascular events.

DISCLOSURE

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REFERENCES

1. Faddy M, Gosden R, Gougeon A, et al. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod 1992; 7(10):1342–6.
2. Burger H, Dudley E, Hopper J, et al. Prospectively measured levels of serum follicle-stimulating hormone, estradiol, and the dimeric inhibins during the menopausal transition in a population-based cohort of women. J Clin Endocrinol Metab 1999;84(11):4025–30.
3. Harlow S, Gass M, Hall J, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10; addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97(4):1159–68.
4. Ellis S, Franks D, Nattrass S, et al. Postreproductive lifespans are rare in mammals. Ecol Evol 2018;8(5):2482–94.
5. He C, Kraft P, Chasman D, et al. A large-scale candidate gene association study of age at menarche and age at natural menopause. Hum Genet 2010;128(5): 515–27.
6. Bae H, Lunetta K, Murabito J, et al. Genetic associations with age of menopause in familial longevity. Menpause 2019;26(10):1204–12.
7. Gold E. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin North Am 2012;38(3):425–40.

8. Castelo-Branco C, Blumel J, Chedraui P, et al. Age at menopause in Latin America. Menopause 2006;13(4):706–12.
9. Kriplani A, Banerjee K. An overview of age of onset of menopause in northern India. Maturitas 2005;52(3–4):199–204.
10. Loh F, Khin L, Saw S, et al. The age of menopause and the menopause transition in a multiracial population: a nation-wide Singapore study. Maturitas 2005; 52(3–4):169–80.
11. Park C, Lim J, Park H. Age at natural menopause in Koreans: secular trends and influences thereon. Menopause 2018;25(4):423–9.
12. McKnight K, Wellons M, Sites C, et al. Racial and regional differences in age at menopause in the United States: findings from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. Am J Obstet Gynecol 2011;205(4):353.e1-8.
13. Gold E, Crawford S, Avis N, et al. Factors related to age at natural menopause: longitudinal analyses from SWAN. Am J Epidemiol 2013;178(1):70–83.
14. Henderson K, Bernstein L, Henderson B, et al. Predictors of the timing of natural menopause in the Multiethnic Cohort Study. Am J Epidemiol 2008;167(11): 1287–94.
15. Morris D, Jones M, Schoemaker M, et al. Familial concordance for age at natural menopause: results from the Breakthrough Generations Study. Menopause 2011; 18(9):956–61.
16. Lawlor D, Ebrahim S, Smith G. The association of socio-economic position across the life course and age at menopause: the British Women's Heart and Health Study. BJOG 2003;110(12):1078–87.
17. Tom S, Cooper R, Kuh D, et al. Fetal environment and early age at natural menopause in a British birth cohort study. Fetal Environ Early Age Nat Menopause a Br Birth Cohort Study 2010;25(3):791–8.
18. Morris D, Jones M, Schoemaker M, et al. Body mass index, exercise, and other lifestyle factors in relation to age at natural menopause: analyses from the breakthrough generations study. Am J Epidemiol 2012;175(10):998–1005.
19. Gold E, Bromberger J, Crawford S, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001; 153(9):865–74.
20. Hyvarinen M, Karvanen J, Pauliina A, et al. Predicting the age at natural menopause in middle-aged women. Menopause 2021;28(7):792–9.
21. Kim C, Cushman M, Kleindorfer D, et al. A review of the relationships between endogenous sex steroids and incident ischemic stroke and coronary heart disease events. Curr Cardiol Rev 2015;11(3):252–60.
22. Price M, Alvarado B, Rosendaal N, 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(5):484–90.
23. Peters S, Woodward M. Women's reproductive factors and incident cardiovascular disease in the UK Biobank. Heart 2018;104(13):1069–75.
24. Ley S, Li Y, Tobias D, 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(11):e006713.
25. Muka T, Oliver-Williams C, Kunutsor S, et al. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. JAMA Cardiol 2016;1(7):767–76.

26. Yoshida Y, Chen Z, Baudier R, et al. Early menopause and cardiovascular risk in women with or without type 2 diabetes: a pooled analysis of 9,374 postmenopausal women. Diabetes Care 2021;44(11):2564–72.
27. Zhu D, Chung H, Dobson A, et al. Type of menopause, age of menopause and variations in the risk of incident cardiovascular disease: pooled analysis of individual data from 10 international studies. Hum Reprod 2020;35(8):1933–43.
28. Zhu D, Chung H, Dobson A, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. Lancet Public Health 2019;4(11):e553–64.
29. Freaney P, Ning H, Carnethon M, et al. Premature menopause and 10-year risk prediction of atherosclerotic cardiovascular disease. JAMA Cardiol 2021;6(12):1463–5.
30. Howard B, Kuller L, Ianger R, et al. Risk of cardiovascular disease by hysterectomy status, with and without oophorectomy: The Women's Health Initiative Observational Study. Circulation 2005;111:1462–70.
31. Lobo R. Surgical menopause and cardiovascular risks. Menopause 2007;14(3 Pt 2):562–6.
32. Matthews K, Gibson C, El Khoudary S, et al. Changes in cardiovascular risk factors by hysterectomy status with and without oophorectomy: Study of Women's Health Across the Nation. J Am Coll Cardiol 2013;62(3):191–200.
33. Rivera C, Grossardt B, Rhodes D, et al. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause 2009;16(1):15–23.
34. Evans E, Matteson K, Orejuela F, et al. Salpingo-oophorectomy at the time of benign hysterectomy: a systematic review. Obstet Gynecol 2016;128(3):476–85.
35. Tepper P, Randolph J, McConnell D, et al. Trajectory clustering of estradiol and follicle-stimulating hormone during the menopausal transition among women in the Study of Women's Health Across the Nation. J Clin Endocrinol Metab 2012;97(8):2872–80.
36. El Khoudary S, Thurston R. Cardiovascular implications of the menopause transition. Obstet Gynecol Clin North Am 2018;45(4):641–61.
37. Lasley B, Crawford S, Laughlin G, et al. Circulating dehydroepiandrosterone sulfate levels in women with bilateral salpingo-oophorectomy during the menopausal transition. Menopause 2011;18(5):494–8.
38. Lasley B, Crawford S, McConnell D. Adrenal androgens and the menopausal transition. Obstet Gynecol Clin North Am 2011;38(3):467–75.
39. Kim C, Harlow S, Zheng H, et al. Changes in dehydroepiandrosterone, androstenedione, testosterone, estrone, and estradiol over the menopausal transition. Women's Midlife Health 2017;3(9). https://doi.org/10.1186/s40695-40017-40028-40694.
40. Stanczyk F, Chaikittisilpa S, Sriprasert I, et al. Circulating androgen levels before and after oophorectomy in premenopausal and postmenopausal women. Climacteric 2019;22(2):169–74.
41. Judd H, Judd G, Lucas W, et al. Endocrine function of the postmenopausal ovary: concentrations of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab 1974;39:1020.
42. Davison S, Bell R, Donath S, et al. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab 2005;90(7):3847.
43. Laughlin G, Barrett-Connor E, Kritz-Silverstein D, et al. Hysterectomy, oophorectomy, and endogenous sex hormone levels in older women: the Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85(2):645–51.

44. Sternfeld B, Wang H, Quesenberry C Jr, et al. Physical activity and changes in weight and waist circumference in midlife women: findings from the Study of Women's Health Across the Nation. Am J Epidemiol 2004;160(9):912–22.
45. Wildman R, Tepper P, Crawford S, et al. Do changes in sex steroid hormones precede or follow increases in body weight during the menopause transition? Results from the Study of Women's Health Across the Nation. J Clin Endocrinol Metab 2012;97(9):1695–704.
46. Matthews K, Crawford S, Chae C, 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(25):2366–73.
47. Sutton-Tyrell K, Wildman R, Matthews K, et al. Sex hormone-binding globulin and the free androgen index are related to cardiovascular risk factors in multiethnic premenopausal and perimenopausal women enrolled in the Study of Women Across the Nation. Circulation 2005;111:1242–9.
48. Samargandy S, Matthews K, Brooks MM, et al. Arterial stiffness accelerates within 1 year of the final menstrual period: the SWAN Heart Study. Arterioscler Thromb Vasc Biol 2020;40(4):1001–8.
49. Kravitz HM, Kazlauskaite R, Joffe H. Sleep, Health, and Metabolism in Midlife Women and Menopause: Food for Thought. Obstet Gynecol Clin North Am 2018;45(4):679–94.
50. Kravitz HM, Janssen I, Bromberger JT, et al. Sleep Trajectories Before and After the Final Menstrual Period in The Study of Women's Health Across the Nation (SWAN). Curr Sleep Med Rep 2017;3(3):235–50.
51. Freeman EW, Sammel MD, Gross SA, et al. Poor sleep in relation to natural menopause: a population-based 14-year follow-up of midlife women. Menopause 2015;22(7):719–26.
52. Mirer AG, Young T, Palta M, et al. Sleep-disordered breathing and the menopausal transition among participants in the Sleep in Midlife Women Study. Menopause 2017;24(2):157–62.
53. Huang T, Lin BM, Redline S, et al. Type of Menopause, Age at Menopause, and Risk of Developing Obstructive Sleep Apnea in Postmenopausal Women. Am J Epidemiol 2018;187(7):1370–9.
54. Colditz G, Willett W, Stampfer M, et al. Menopause and the risk of coronary heart disease in women. N Engl J Med 1987;316(18):1105–10.
55. The North American Menopause Society. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 2017;24(7):728–53.
56. Rossouw J, Anderson G, Prentice R, 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(3):321–33.
57. Sprague B, Trentham-Dietz A, Cronin K. A sustained decline in postmenopausal hormone use: results from the National Health and Nutrition Examination Survey, 1999-2010. J Obstet Gynecol 2012;120(3):595–603.
58. Marjoribanks J, Farquhar C, Roberts H, et al. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev 2017;1(1):CD004143.
59. Anderson G, Limacher M. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initative randomized controlled trial. JAMA 2004;294(14).
60. Manson J, Allison M, Rossouw J, et al. Estrogen therapy and coronary-artery calcification. 356. N Engl J Med 2007;25:2591–602.

61. Hodis H, Mack W, Henderson V, et al. Vascular effects of early versus late postmenopausal treatment with estradiol. N Engl J Med 2016;374(13):1221–31.
62. Sriprasert I, Hodis H, Karim R, et al. Differential effect of plasma estradiol on subclinical atherosclerosis progression in early vs. late postmenopause. J Clin Endocrinol Metab 2019;104(2):293–300.
63. El Khoudary S, Venugopal V, Manson J, et al. Heart fat and carotid artery atherosclerosis progressin in recently menopausal women: impact of menopausal hormone therapy. The KEEPS Trial. Menopause 2020;27(3):255–62.
64. Harman S, Black D, Naftolin F, et al. Arterial imaging outcomes and cardiovascular risk factors in recently menopausal women. Ann Intern Med 2014;161:249–60.
65. El Khoudary S, Zhao Q, Venugopal V, et al. Effects of hormone therapy on heart fat and coronary artery calcification progression: secondary analysis from the KEEPS trial. J Am Heart Assoc 2019;8(15):e012763.
66. Oliver-Williams C, Glisic M, Shahzad S, et al. The route of administration, timing, duration and dose of postmenopausal hormone therapy and cardiovascular outcomes in women: a systematic review. Hum Reprod Update 2019;25(2):257–71.
67. Schierbeck L, Rejnmark L, Tofteng C, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: a randomised trial. BMJ 2012;345:e6409.
68. Manson J, Aragaki A, Bassuk S, et al. Menopausal estrogen-alone therapy and health outcomes in women with and without bilateral oophorectomy: a randomized trial. Ann Intern Med 2019;171(6):406–14.
69. Davis SR, Baber R, Panay N, et al. Global Consensus Position Statement on the Use of Testosterone Therapy for Women. J Clin Endocrinol Metab 2019;104(10):4660–6.
70. Islam RM, Bell RJ, Green S, et al. Safety and efficacy of testosterone for women: a systematic review and meta-analysis of randomised controlled trial data. Lancet Diabetes Endocrinol 2019;7(10):754–66.
71. Zhu T, Goodarzi MO. Causes and consequences of polycystic ovary syndrome: insights from Mendelian randomization. J Clin Endocrinol Metab 2022;107(3):e899–911.
72. Coleman R, Stevens R, Retnakaran R, et al. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007;30:1292–3.
73. Goff D Jr, Lloyd-Jones D, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl 2):S49–73.
74. Rossouw J, Prentice R, Manson J, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA 2007;297(13):1465–77.
75. Salpeter S, Cheng J, Thabane L, et al. Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. Am J Med 2009;122:1016–22.
76. The 2022 Hormone Therapy Position Statement of the North American Menopause Society Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause 2022;29(7):767–94.
77. Tepper P, Brooks M, Randolph J Jr, et al. Characterizing the trajectories of vasomotor symptoms across the menopausal transition. Menopause 2016;23(10):1067–74.

78. Burgos N, Cintron D, Latortue-Albino P, et al. Estrogen-based hormone therapy in women with primary ovaria insufficiency: a systematic review. Endocrine 2017; 58(3):413.
79. Upton C, Daniels J, Davies M. Premature ovarian insufficiency: the need for evidence on the effectiveness of hormonal therapy. Climacteric 2021;24(5):453–8.
80. Wierman M, Arlt W, Basson R, et al. Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2014; 99(10):3489–510.