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Review

# Women's Heart Health and the Menopausal Transition: Two Faces of the Same Coin

Colleen M. Norris, PhD, RN, MSc, FAHA, FCAHS,[a,b,c] Nicole L. Tegg, RN, MN, BScN,[a] Sofia B. Ahmed, MD, MSc,[c] Sharon Gingara,[d] Bobbi-Jo Green, BEd,[d] Colleen Gresiuk, RN, BScN, CNCCP(c),[e] Maya Henriquez, RN, MN, BScN,[a] Sharon L. Mulvagh, MD, FRCPC,[f] Andrea Van Damme, MN, NP, BScN, RN,[g] Caitlynd Myburgh, PhD, MSc, BSc Hons, BSc,[a,h] and Michelle M. Graham, MD[g]

[a] *Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada*

[b] *Cavarzan Chair in Mature Women's Research, WCHRI, AWHF, Edmonton, Alberta, Canada*

[c] *Faculty of Medicine, School of Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada*

[d] *Member of Canadian Women's Heart Health Alliance with lived experience, Edmonton, Alberta, Canada*

[e] *University of Alberta Hospital, Edmonton, Alberta, Canada*

[f] *Dalhousie University, Halifax, Nova Scotia, Canada*

[g] *Division of Cardiology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada*

[h] *Faculty of Natural Sciences, The Kings University, Edmonton, Alberta, Canada*

**ABSTRACT**

**The impact of the presence or absence of sex hormones on women's health is woefully underresearched. Fundamentally, women's bodies are now understood to spend considerable time under widely fluctuating hormonal influences, including puberty, pregnancy, peripartum, and menopause, and a woman's vessels are therefore *preset* for functional and physiological alterations based on levels of sex hormones. However, our understanding of the influences of sex hormones on the regulation of a multitude of biological and physiological processes has not translated into the development and/or collection or analyses of data on therapeutic treatments and/or outcomes in the context of women's disease management.**

**RÉSUMÉ**

**Les effets sur la santé des femmes associés à la présence ou à l'absence d'hormones sexuelles ont fait l'objet de trop peu d'études. On sait essentiellement que les taux d'hormones fluctuent considérablement tout au long des étapes de la vie des femmes, qu'il s'agisse de la puberté, de la grossesse, de la période périnatale et de la ménopause, et que leurs vaisseaux sont en fait *préréglés* pour permettre diverses modifications fonctionnelles et physiologiques en fonction du taux d'hormones sexuelles. Cependant, notre compréhension de l'influence des hormones sexuelles sur la régulation d'une multitude de processus biologiques et physiologiques ne s'est pas traduite par la collecte et/ou l'analyse de données sur les traitements ou les résultats thérapeutiques dans le contexte de la prise en charge de diverses maladies chez les femmes.**

### *Lay Summary*

*Women's bodies are subject to changing hormonal levels throughout their lives. However, how hormonal changes affect health and disease is poorly understood. This paper reviews the history of the relationship between the time at which hormone therapy is started and the start of menopause (the timing hypothesis), to improve cardiovascular care for women during menopause.*

Estrogens (sex steroid hormones) display a broad spectrum of physiological functions that include but are not limited to the regulation of the menstrual cycle and reproduction, bone density, brain function, cholesterol mobilization, and the control of inflammation. Specifically, from a vascular perspective, sex hormones are known to exert effects on vascular reactivity via the endothelium and directly on smooth

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Corresponding author: Dr Colleen M. Norris, Faculty of Nursing, 3rd Floor ECHA, University of Alberta, Edmonton, Alberta T6G 1C9, Canada. Tel.: +1-780-492-0784.

E-mail: cnorris@ualberta.ca

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muscles. In their 2008 review of the vascular implications of estrogens, Miller et al. noted that although the impact of estrogen exposure in preventing or treating cardiovascular disease (CVD) is controversial, estrogen clearly has important effects on vascular physiology and pathophysiology, with potential therapeutic implications.[1] Research specific to the menopausal transition (MT),[2] from the postreproductive phase through perimenopause, menopause, to postmenopause, recognizes the fluctuations and reductions that result in many estrogen-related musculoskeletal, metabolic, neurologic, and vascular responses. Yet, a dearth of information is available on caring for women's heart health in the context of the MT of midlife women. Therefore, the purpose of this paper is to review the history of the relationship among menopause, hormone therapy, and the "timing hypothesis," as well as the literature on cardiovascular care for women in the context of the MT.

## The History of Hormone Replacement and Its Relationship to CVD Care in Women

In a seminal chapter on the history of menopause, Geraghty chronicles that, concurrent with the field of endocrinology, general medicine began to focus on the epidemiology of "age-related diseases."[2] In particular, interest increased regarding the association of chronic diseases such as osteoporosis and CVDs that were attributed to ovarian vascular changes or the "failure of the ovaries" in women. As a result, the "stages" of the MT were reduced to the binary term "menopause," which was defined as an age-related "disease," with treatment targets focused on the deficiency of estrogen. Furthermore, the use of hormones to prevent diseases thought to be due to the "failure of the ovaries" or postmenopause became obligatory in Western medicine.[2] By 1975, estrogen became the most commonly prescribed drug in the US.[3] The critical turning point in the use of exogenous hormones for women occurred with an editorial published in 1975 in the *New England Journal of Medicine*, followed by 2 studies showing an increased risk of endometrial cancer in postmenopausal women.[4-6] These studies attracted researchers' attention and resulted in the initiation of studies and societies, and evidence began to emerge. Research on other health issues in menopausal women began to surface, including breast cancer, myocardial infarction (MI), and thromboembolic events.

## The Women's Health Initiative

By the time the Women's Health Initiative (WHI) was initiated in 1991, hormone replacement therapy (HRT) was thought to be universally beneficial in the prevention of osteoporotic fractures and coronary heart disease, and the results of the WHI were believed to justify women staying on HRT for life. Postmenopausal women (mean age 63.5 years) with an age-related increased risk of heart disease were included in the study. The 4 arms of the WHI randomized controlled trial (RCT) study included the following: arm 1—8506 women (with a uterus) using conjugated equine estrogen (CEE) and medroxyprogesterone acetate—vs arm 2—placebo (n = 8102)[7]—and arm 3—5310 women who had had a hysterectomy who were taking CEE alone—vs arm 4 (n = 5429)—placebo.[8] The CEE—medroxyprogesterone acetate arm (arm 1) of the study was stopped early (1996) when a slight increase in breast cancer was detected in the hormone group. The data reported in 2004 on the CEE-alone arm (arms 3 and 4) identified no increased risk of breast cancer. However, the increased risk of stroke and venous thromboembolism (VTE) in both groups also prompted the discontinuation of the CEE-alone arm (arm 3). The effect of the results of the WHI were dramatic. The usage rate of HRT dropped from approximately 40% of women in their 50s and 30% of women in their 60s in the year 2000, to 7% of women in both age groups in 2010.[2]

Following the premature discontinuation of the WHI and the reported CVD risk, a number of age-stratified post hoc studies were performed, reporting that women aged 50-59 years had actual *beneficial and protective* effects for CVD.[9] Geraghty notes that although the public and clinicians sought a "yes or no" answer to the question of whether to use HRT, the largest contribution of the WHI was the recognition of the complexity of patient selection and the TIMING and DURATION of hormone use in relation to its risks and benefits.[2] Most important, no distinction was made in the WHI study between late menopause use (average age of participants in the WHI was 63.5 years) and hormone use during the MT (women aged 50-59 years).

In 2006, Salpeter et al. reported a meta-analysis of 23 RCTs looking at menopausal hormone therapy (MHT) and its effects on coronary heart disease (MI and cardiac death) in 39,049 younger (mean time at baseline from menopause $< 10$ years) and older postmenopausal (mean time at baseline from menopause $\geq 10$ years) women. The results identified that MHT significantly *reduced* events in younger women (odds ratio 0.68, 95% confidence interval 0.48-0.96) but NOT in older women (odds ratio 1.03, 95% confidence interval 0.91-0.96).[9,10] These data gave rise to the "timing hypothesis."

## The Timing Hypothesis

The timing hypothesis was proposed by Professor Thomas Clarkson based on his work on atherosclerosis in menopausal monkeys.[9] Clarkson demonstrated that the time at which hormone therapy is started in relation to when menopause starts determines its effects on the progression of coronary artery stenosis.[11] Giving estrogen immediately after surgical menopause (oophorectomy) in monkeys reduced coronary artery atherosclerosis by 70%. When the administration of estrogen was delayed by 2 years after oophorectomy (equal to 6 human postmenopausal years), no reduction occurred in coronary artery atherosclerosis. Moreover, the delay in MHT in postmenopausal monkeys allowed the progression of atherosclerosis with plaque instability that approximated the same phenomenon in humans aged 60-65 years, which was the dominant group in the WHI.[9] The timing hypothesis proposed that the benefits of MHT, specifically estrogen's effect of preventing atherosclerosis, occur when MHT is initiated before the reduction of the well-documented effects of endogenous estrogen on healthy endothelium, including (i) vasodilation, (ii) decreased inflammation, and (iii) decreased lesion progression due to increases in nitric oxide, decreased inflammatory cell adhesion, decreased platelet aggregation,

decreased vascular smooth muscle cell proliferation, and decreased low-density lipoprotein oxidation and binding.[9,12] Furthermore, once the endothelium has been deprived of endogenous estrogen and is transformed by atherosclerosis, the effects of the administration of exogenous estrogen MHT become deleterious, as the estrogen receptors have decreased expression and/or function, leading to decreased vasodilatation, increased inflammation, and increased neovascularization.

## The KEEPS and ELITE Trials

Two RCTs, the **K**ronos **E**arly **E**strogen **P**revention **S**tudy (KEEPS)[13] and **E**arly versus **L**ate **I**ntervention **T**rial With **E**stradiol (ELITE)[14] trials were designed to test the timing hypothesis that the initiation of MHT (oral CEE in KEEPS and oral estradiol in ELITE) in healthy early postmenopausal women would slow the progression of atherosclerosis. The KEEPS trial demonstrated that the hormone formulations provided did NOT delay the progression of atherosclerosis (the annual increase in carotid artery intimal medial thickness (CIMT) of 0.007 mm per year), with similar findings across all 3 treatment groups. Paciuc writes that some felt this was from "too low a dose of estrogen, acting on too healthy a population, for too short a time."[9] An important finding, however, is that in both the oral and transdermal estrogen treatment arms of the KEEPS study, women reported reductions in hot flashes, improved sleep, and maintenance of bone density, with no adverse events, including venous thromboembolisms.[9,13] Furthermore, a sexual function substudy of KEEPS[15] reported improvements in both physical and emotional domains of sexual function in both the oral estrogen and the transdermal estrogen arms, compared with placebo.

The ELITE trial included 643 postmenopausal women stratified into 2 groups according to the time since menopause. After a median 5-year follow-up, a significant difference was reported in the effect of estradiol on CIMT progression between the early ($<$ 6 years postmenopause) vs late groups ($>$ 10 years postmenopause; $P = 0.007$ for the interaction).[14] In the early group, CIMT progression increased significantly more in the placebo group, compared to the MHT group. In contrast, the rates of CIMT progression in the placebo and estradiol groups in the later menopause group were similar. Post-trial analysis reported that higher serum estradiol levels were inversely associated with CIMT progression in the early group and were positively associated with CIMT progression in the late group. The investigators concluded that "these results not only support the HT timing hypothesis . . . but also add an explanatory mechanism consistent with the timing hypothesis."[9,13,14] If the timing hypothesis is the final arbiter in the historical dispute over MRT, then the results of these RCTs suggest that when an indication is present for MRT without contraindications, then it should be initiated in women who are younger than 60 years or within the first 10 years of the MT.[9] More importantly, Maas et al., in a (2021) report on a recent meta-analysis of RCT data, as well as data from a Finnish registry, confirm that initiating MHT, both oral and transdermal within 10 years of the onset of menopause, significantly reduces MIs and deaths, by 50%, whereas discontinuation of MHT results in a transient risk of coronary death, thereby supporting the preventative effect of MHT on CVDs in women.[16]

## The Interaction of the MT and CVD Risk and CVDs

The beliefs and science surrounding the MT continue to influence every aspect of women's midlife healthcare today. Attitudes relating to the MT life stage influence women's symptom profiles, health-seeking behaviours, and importantly, the clinical training and resulting interactions of health professionals and midlife women. However, most women assume that menopause-related changes will happen around the age of 50 years, and only 13% assume changes begin before age 44 years.[17] Although women may be prepared for puberty and childbirth, little to no information and/or education is available about the MT, and women do not know when to attribute symptoms to hormonal changes.[17] Moreover, younger women (age 35-55 years) and clinicians have been taught to assume that women are not at risk for CVDs before menopause.[17] Ironically, the signs and symptoms that are more common in younger women with heart health issues, including chest discomfort, sweating, nausea, shortness of breath, and lightheadedness, are frequently attributed to being "symptoms" of perimenopause. Sex steroid—associated events, such as early or late menarche, very irregular menstrual cycles at ages 20-35 years, and premature menopause (at age $<$ 40 years) are now recognized as being associated with an increased risk of early CVD, but a gap remains in our understanding of the relationship and/or risks associated with women's experiences with CVDs throughout the MT.

### CVDs and increased prevalence in women

The term CVDs is an inclusive term reflecting a number of vascular conditions, including hypertension, atherosclerosis, cerebrovascular disease, ischemic heart disease, and cardiac failure. Current evidence and a growing knowledge of the patterns of ischemic heart disease (IHD) in younger women suggest that we should be better able to recognize, diagnose, and treat symptomatic women. However, as identified in a 2023 Heart & Stroke Canada report, half the women who experience an MI have their symptoms go unrecognized, and every 16 minutes, a woman in Canada dies as a result of heart disease or stroke.[18] Alarmingly, the number of women under age 65 years with an MI is increasing, especially type II MIs with nonobstructive coronary arteries (MINOCA), which is at least twice as prevalent in women as it is in men.[16] The Heart & Stroke Canada report[18] identifies that the signs and symptoms of IHD for women, such as angina, are more likely to be due to ischemia with nonobstructive coronary arteries (INOCA), which is more common in younger women. Coronary vasomotor disorders, such as coronary artery spasm and coronary microvascular dysfunction, represent a major cause of IHD in middle-aged women.[16] As well, spontaneous coronary artery dissection (SCAD) is a common cause of heart attacks in younger women, with 90% of SCAD patients being women.[19] SCAD has been reported to account for 25% to 30% of all heart attacks in women under age 60 years[16,20]—in other words, women in the MT.

### Benefits and risks of estrogen exposure

General estrogenic actions and the benefits and risks of estrogen exposure on vascular physiology and pathophysiology have been determined primarily through cohort and/or registry data for women whose age at menopause was > 45 years, and/or for women with early menopause (at age < 45 years) and women with premature ovarian insufficiency (at age < 45 years) who are on HRT.[14] Consequently, Maas et al. reported that the "possible mechanisms" mediating the CVD benefit of MHT (especially transdermal MHT) include insulin sensitivity, improvements in the lipid profile and body composition, decreases in blood pressure in the case of progestin-containing regimens, and a direct vasodilatory and anti-inflammatory effect.[16] Further, although healthy endothelium is sensitive to the vasodilator properties of estrogens, this sensitivity is reversed when vascular stiffness and atherosclerotic disease develop over time. Evidence indicates that hypoestrogenic environments promote early development of atherosclerosis, impaired endothelial function, and CVD[2,16]; however, although CVD risk increases with menopause, this effect cannot be distinguished from that of aging.[14] Another important point to note is that studies to date have focused on the menopausal experiences of educated white women in the global north, with few if any studies including other populations of women. Augmenting the dearth of evidence on the effects of fluctuations in sex-steroid levels on a women's vascular system is the reality that MT education and the influence of sex steroids on women's midlife health is either absent or extremely limited in medical, nursing, and allied health curricula. Content on women's health—more specifically, women's heart health—is missing in most cardiovascular textbooks and conferences, or it is relegated to "special interest" sections and/or sessions.

This significant gap in our understanding of the interaction of the MTs and women's heart disease has led to a paradox of sorts, whereby clinicians and women alike attribute the symptoms a woman describes as being related to either the MT and sex steroid−level changes ***OR*** female-pattern CVDs. Hodis et al. note that the decline in endothelial function starts in early menopause, even before signs of subclinical atherosclerosis are present.[14] This mechanism, which may be part of the pathophysiology of chest pain and dyspnea of "undetermined" origin,[14] is described by women with lived experience in the Canadian Women's Heart Health Alliance Atlas, chapter 3, "Stopped at the Gate" and is frequently mistakenly labelled as being a sign of "stress" or as "menopausal symptoms." [14,21] Important to note is that although evidence linking vasomotor symptoms to CVD is limited , hot flashes and/or flushes, cold sweats and night sweats, the classic menopausal symptoms, are linked to CVD risk factors and subclinical CVD,[22] and they may be an important harbinger of female-specific CVD.

## Moving Forward

A clear finding is that the impact of aging and environmental and/or behavioural risk factors interact with changes in the sex steroids during the MT. Increasing hypoestrogenism is linked to increased adiposity in the absence of weight gain or changes in physical activity, increased total cholesterol, and altered endothelial cell function that leads to increased vascular inflammation and decreased vascular elasticity.[2] Moreover, increase in risk contributed by the diminishment of sex steroids and by age may not be constant and may be influenced by other female-specific risk factors, including complications of pregnancy, and/or endocrine and gynecological conditions, such as polycystic ovarian syndrome and endometriosis. These are risk factors for CVD, and yet women consistently report that the ONLY question they are asked regarding the fundamental influence of sex steroids on women's health, whether accessing primary or acute care, is "When was your last menstrual period?"

### (A) Assessment of the contribution of sex-specific risk factors in the context of CVD in women

It is imperative that all women's heart health assessments include the collection and documentation of sex-specific risk variables related to hormonal and reproductive status known to be associated with CVD risk. The 2021 consensus document from the European Society of Cardiology entitled "Cardiovascular Health After Menopause Transition, Pregnancy Disorders, and Other Gynaecologic Conditions" succinctly outlines sex-specific risk factors of which the collection is essential to identifying the contributions of sex-specific risk factors in the context of CVD in women (see Fig. 1).[16]

### (B) Apply the latest guidance and/or evidence specific to CVD and women during the MT

In December 2021, the Society of Obstetricians and Gynaecologists of Canada (SOGC) created a guideline,[23] with the objective of providing strategies for improving the care of perimenopausal and postmenopausal women. The summary statements provide clinical guidance and evidence specific to CVD and women who are in the MT. The summary statements include the following:

- *Women who initiate menopausal hormone therapy shortly after menopause are, in general, at low risk for events in the next few years (high). Evidence supports aggressive identification and modification of risk factors as the most effective means of reducing cardiovascular risk (high).*
- *Women who initiate menopausal hormone therapy 10 or more years after menopause are at increased risk for adverse cardiac events (high).*
- *With respect to stroke, increased risk has been identified in all age groups using standard formulations of menopausal hormone therapy; however, the incidence in young women is extremely low (low).*
- *Incidence of venous thrombotic events increases with age (> 60 years) and body mass index (BMI), even in otherwise healthy women; menopausal hormone therapy increases the risk (high).*
- *Menopausal hormone therapy is not indicated for primary or secondary prevention of cardiovascular disease (moderate).*
- *Women with premature or early-onset menopause appear to be at an increased risk of adverse cardiovascular outcomes, and this risk may be prevented by the use of menopausal hormone therapy until the average age of menopause (moderate).*

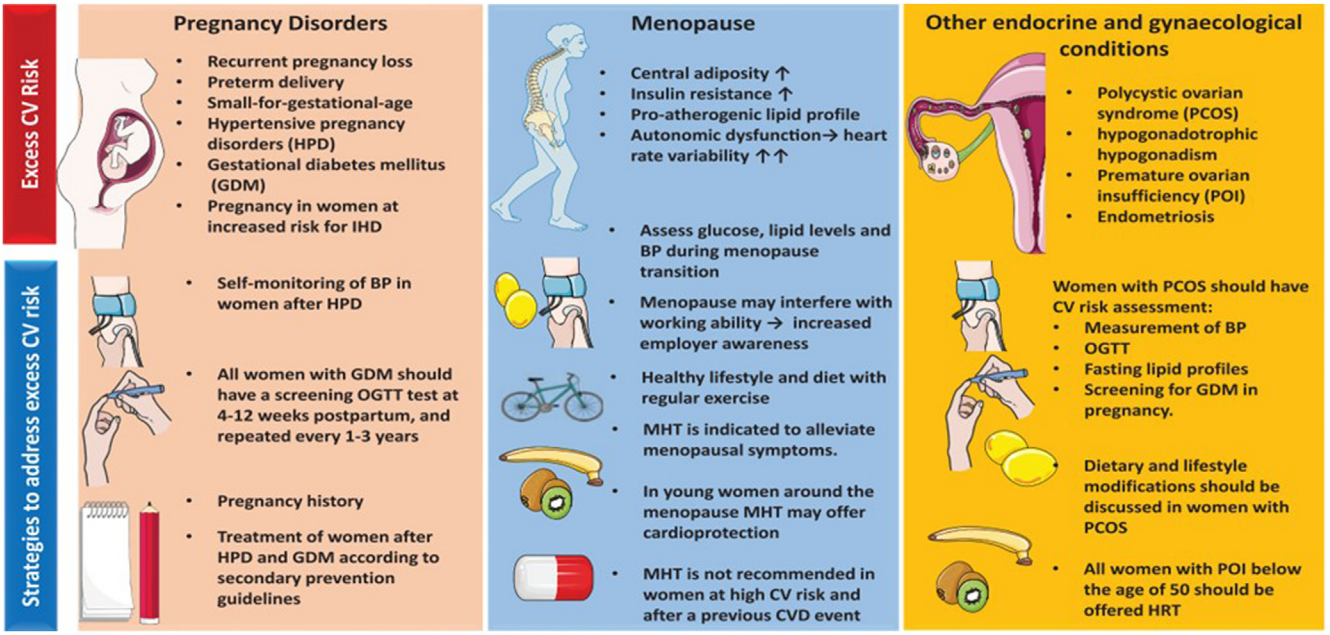


**Figure 1.** Female-specific risk factors and strategies for prevention. BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; HRT, hormone replacement therapy; IHD, ischemic heart disease; MHT, menopausal hormone therapy; OGTT, oral glucose tolerance test. Reproduced with permission from Oxford University Press on behalf of the European Society of Cardiology from Maas AH, et al.[16]; permission conveyed through Copyright Clearance Center, Inc.

- *Menopausal hormone therapy increases the risk of venous thromboembolism; oral and combined hormone therapy preparations are more closely associated with risk of venous thromboembolism than either with transdermal preparations or estrogen alone (moderate).*
- *There is a lack of high-quality data to provide guidance on the impact of routes of estrogen administration on the risk of venous thrombotic events or cardiovascular disease (low).*

More recently, a review in the *Canadian Medical Association Journal* entitled "A Pragmatic Approach to the Management of Menopause," reported that, despite early concerns, increasing evidence shows a possible reduction in coronary artery disease with MHT among patients who start MHT before age 60 years or within 10 years of menopause.[24] Furthermore, they note that both RCTs and observational studies consistently show that an association exists between MHT and reductions of coronary artery disease events among women. Lega et al. note that the metabolic benefits of MHT include an improvement in lipid profile (an increase in high-density lipoprotein and a decrease in low-density lipoprotein) and that some studies have suggested an improvement in insulin sensitivity with a reduction in the risk of diabetes.[24]

### (C) Document the progression of women + stage of the MT

Finally, given the heterogeneity of the progression of women+ (including transgender men and nonbinary people) through the MT, it is important for both clinicians and the women they partner with in healthcare to understand and document (Fig. 2) where they are in the MT. The stages of the MT are normal, and women who are experiencing symptoms are not "ill." Staging tools, such as the Straw 10+, do scale subtle changes in flow and length of menstrual cycles, vasomotor symptoms— including feelings of heat with flushing, cold sweats, and night sweats—sleep disturbances, and mood/cognition changes—including irritability, tearfulness, insomnia, memory/concentration issues, depression, anxiety, and stress—identified in the Menopause Rating Scale.[25] However, these factors are all suggestive of perimenopause and left untreated may contribute to an increased cardiovascular risk and overall health concerns.

## Conclusion

The gap in understanding of the relationship between the MT and CVDs in women has meant that women with heart health issues continue to be under-researched, under-diagnosed, undertreated, under-supported, and under-aware. The widespread, consistent assessment and collection of both women's CVD risk factors as well as MT factors, including menopausal stage and symptoms, is the first step toward understanding women's heart health that may be applied to determining the most effective way to prevent, diagnose, and/or treat CVDs in women.

## Ethics Statement

Research reported has adhered to relevant ethical guidelines.

## Patient Consent

As this is a review of the research on women's CVD and the menopausal transition literature the authors confirm that patient consent is not applicable to this article.

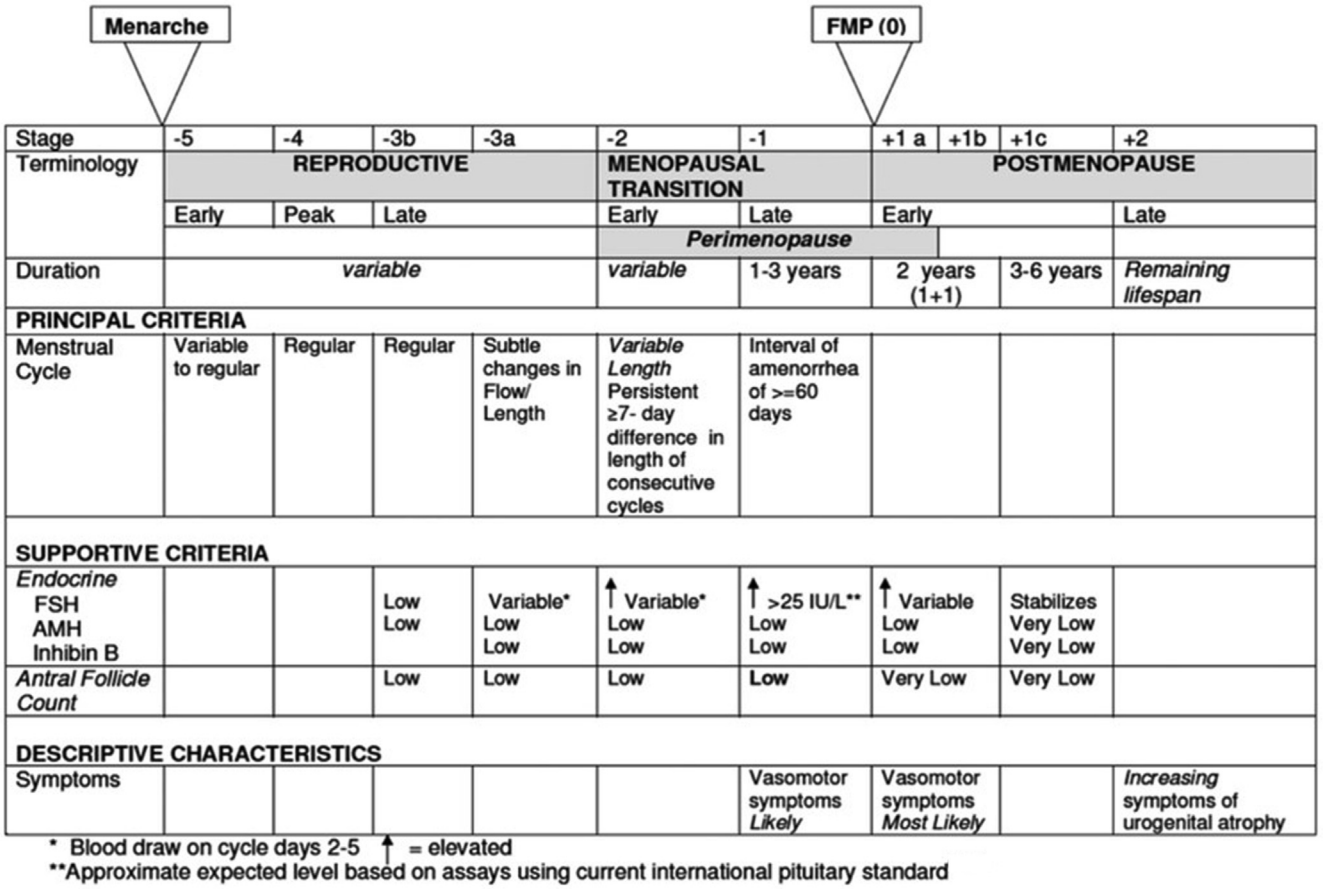


**Figure 2.** The Stages of Reproductive Aging Workshop + 10 staging system for reproductive aging in women. AMH, anti-Mullerian hormone. FMP, final menstrual period; FSH, follicle-stimulating hormone; IU, international units. Reproduced with permission from The North American Menopause Society from Harlow et al.[26]; permission conveyed through Copyright Clearance Center, Inc.

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