

Menopause and Cardiovascular Disease: Endogenous Reproductive Hormone Exposure affects Risk Factors

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In the United States, absolute mortality due to cardiovascular disease (CVD) is on the rise, and CVD is responsible for up to 45% of all deaths in women.¹ Modifiable risk factors, including dyslipidemia, obesity and hypertension, account for up to 94% of all incident cases in women, according to the INTERHEART study of myocardial infarction risk factors in 52 countries.² Our ability to intervene in this surge in CVD cases is hampered, in part, by incomplete knowledge of the relationship between reproductive aging and cardiovascular risks.

While younger women are rarely affected, CVD prevalence is significantly increased in the sixth decade of life. Menopause and its underlying estrogen deficiency are often implicated, yet the supposed menopause-related trend parallels a similar upswing in men of the same age (Figure, page 22).³ The influence of endogenous reproductive hormones should be distinguished from chronological aging and other coexistent morbidities. Quantitative assessment of the reproductive hormone axis in relationship to CVD risk factors is a

promising strategy that may lead to identifying potential targets for intervention.

The Menopause Transition

The menopause transition represents a dynamic endocrine process that occurs at a different pace in each individual. Menstrual irregularity heralds the beginning of early perimenopause and is defined as variable cycle length that differs from usual by more than 7 days.⁴ Evidence is emerging that not all irregular cycles are created equal.

Based on a recent report from the Study of Women's Health across the Nation (SWAN),⁵ an ongoing multiethnic cohort that began in 1994 as an investigation of women traversing menopause, the neuroendocrine underpinnings of the menopause transition involve insensitivity of the hypothalamus to estrogen, with loss of negative and positive estrogen feedback. Clinically, perimenopausal women exhibiting neither estrogen increase nor luteinizing hormone (LH) surge appear to have more menopausal symptoms (Table 1, page 22). Given these data, defining subsets of perimenopausal women by menstrual cycle patterns and hormonal profiles is a promising tool for identifying susceptibility to increased cardiovascular risks.

Estrogen has many effects on the cardiovascular system, including a favorable lipid profile, vasodilatation, and inhibition of the development and progression of atherosclerotic lesions.⁶ While this overall cardiovascular profile of endogenous estrogen appears beneficial, one must not infer that estrogen deficiency is a CVD culprit without having sound epidemiologic evidence. Menstrual

cycle irregularity has been suggested as a risk factor for CVD in a review of 28 pertinent studies dated 1958-1998.⁷ The menopause transition is associated with some changes in the lipid profile, as shown by several cohort studies.⁸ However, the generalizability of these studies is restricted by limited ethnic diversity of the participants, scant hormone data and a dearth of information on hemostatic risk factors.

Update from SWAN

A detailed examination of the indices of reproductive function and CVD risk factors was recently undertaken in 500 menstruating perimenopausal women.⁹ This report represents a subcohort analysis from SWAN. Data from the Daily Hormone Study (DHS) were contrasted with CVD risk factors. Quantitative analysis of endogenous reproductive hormones across one menstrual cycle was performed.

A major strength of this study is the ability to characterize menstrual cycles of perimenopausal women by measuring daily hormone activity. Reproductive function was assessed via several distinct parameters: evidence of presumed ovulation, length of the ovulatory cycles and reproductive competence of the ovary. Three hypotheses were formulated *a priori*: (1) nonovulatory cycles confer a greater risk of CVD, (2) longer ovulatory cycles are associated with a detrimental CVD risk profile, and (3) a reproductively competent ovary is associated with the most beneficial CVD risk profile.

The study population consisted of mostly early perimenopausal

women (mean age, 47.1 years) from six major US metropolitan areas. Most participants were high school graduates (77%), with a diverse ethnic make-up: African-American (21%), Caucasian (31%), Chinese (18%), Japanese (22%) and Hispanic

(7%). (Percentages did not add up to 100% due to rounding.) A majority of the subjects (71%) reported menstrual irregularity within the last year; however, 84% of the women had evidence of luteal activity and a mean cycle length of 28 days.

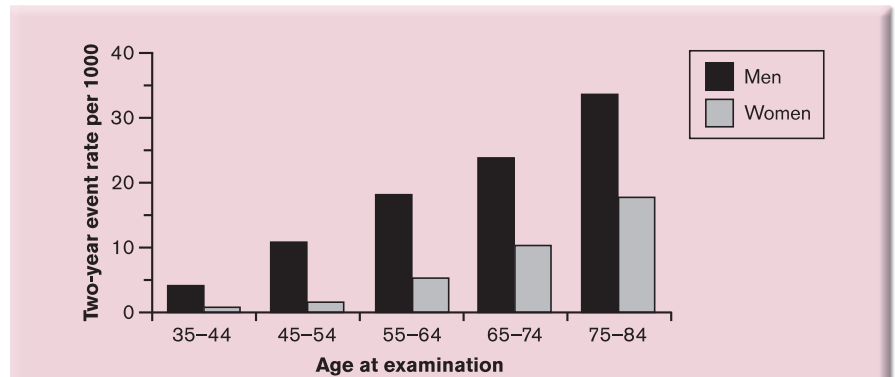


Figure. Incidence of myocardial infarction in men and women by age and sex in a 26-year follow-up in the Framingham study. Note that the incidence increases with age in both sexes, but occurs later (primarily after menopause) in women.

(Data from Lerner DJ, Kannel WB. *Am Heart J* 1986;111:383.³)
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Table 1. Menopause Symptoms in Perimenopausal Women with Presumably Anovulatory Cycles: Data from SWAN Subcohort of Annual Daily Collection of First Morning Urine for an Entire Menstrual Cycle or up to 50 Days*

	Loss of negative feedback only	Loss of positive and negative feedback	Loss of ovarian function	P value
Hormone profile	↑E ₂ ↑LH	↑E ₂ only	No E ₂ or LH	
Number of women	28	31	97	
Hot flashes or night sweats (mean % of days/cycle)	9	11	26	.009
Women not experiencing hot flashes or night sweats (mean % of days/cycle)	54	48	34	.14

E₂ = estradiol; LH = luteinizing hormone
 *Modified from Weiss G, Skurnick JH, Goldsmith LT, et al, 2005.⁵

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Several well-established and emerging risk factors for CVD were measured, including metabolic parameters (insulin, lipids, lipoproteins and triglycerides), hemostatic and inflammatory factors, blood pressure, body mass index (BMI) and waist circumference. Urinary gonadotropins (LH and follicle-stimulating hormone) and estrogen and progesterone metabolites were evaluated from daily urine collection of the entire menstrual cycle, or up to 50 days if there was no bleeding. The samples were frozen by the participants at home until the full collection was handed over for evaluation.

Results. Luteal activity was determined by sustained elevation in urinary progesterone metabolites based on an established algorithm. There were few differences in the risk-factor profile based on luteal status. When BMI was taken into account, ovulating women had lower diastolic blood pressure and fibrinogen (two of 16 potential risk factors assessed).

Women with luteal activity ($n=420$) were further subdivided into three groups based on cycle length: short (≤ 24 days), intermediate (25–32 days) and long (≥ 33 days). Notably, longer cycle length was significantly correlated with 11 risk factors (Table 2, page 24). After adjustment for BMI, this association remained significant only for triglycerides and C-reactive protein.

Reproductive competence was defined as high follicular estrogen and high luteal progesterone. After BMI adjustment, higher follicular estrogen metabolite concentrations were inversely associated with waist circumference, triglycerides, lipoprotein (a), insulin and plasminogen activator

inhibitor (PAI-1). Ethnic variation, independent of the effect of age and BMI, was noted in the relationship of estrogen metabolites with lipoprotein (a) and PAI-1, wherein lower estrogen metabolites were associated with higher levels of lipoprotein (a) and PAI-1 among Caucasian and Chinese women. After BMI adjustment, higher daily luteal progesterone metabolites were significantly associated with tissue type plasminogen activator-antigen (tPA-ag). Unexpectedly, follicular progesterone metabolites were inversely associated with waist circumference, triglycerides, insulin, PAI-1, tPA-ag and factor VII.

Analysis. Excess body weight is a strong predictor of diminished reproductive hormone secretion and CVD risk factors. In an earlier SWAN report from a larger cohort,¹⁰ obesity was significantly associated with longer cycle length and lower urinary levels of gonadotropins and progesterone metabolites. Preliminary results from a frequent serum sampling study¹¹ indicate that ovu-

lating obese women exhibit a unique phenotype of hypogonadotropic hypogonadism. One may only expect worsening of this trend given that the obesity epidemic shows no signs of abating.

As expected, higher daily estrogen metabolite levels were associated with a favorable CVD risk profile in the subcohort analysis from SWAN.⁹ This may be taken to support the third hypothesis of the study; namely, that a reproductively competent ovary appears to be protective on a cardiovascular level. Follicular progesterone metabolites could result either from delayed excretion from the preceding menstrual cycle (which may be indicative of high rates of progesterone production in the prior luteal phase) or they may come from the adrenal glands.

Adding strength to the observed results was not only the statistical significance of many of estrogen's associations with risk factors, but also the considerable magnitude of those associations. Longer cycles in women with luteal activity were associated with a 20-mg/dL increase in triglycerides (age and BMI-adjusted $P=0.005$). Notably, ethnic variation between estrogen levels and metabolic and hemostatic factors may play a role in the variable elevation of CVD risks among individuals from different backgrounds.

In summary, BMI-independent connection between the sex steroid metabolites and hemostatic and metabolic risk factors provides unique information that could help to clarify why the rates of CVD increase dramatically after menopause (Table 2, page 24).

Future Directions: Clinical Implications

The newly established association of urinary sex steroid metabolites with CVD risk factors provides an important insight into the relationship between the hypothalamic-pituitary-gonadal and metabolic axes. Reproductive aging occurs concurrently with, and may mediate, a predisposition to CVD; however, underlying mechanisms remain unclear. The influence of adiposity on reproductive and metabolic systems may affect some of the increased risk seen after menopause. As the incidence of CVD increases in the aging SWAN cohort, further follow-up of these women promises to uncover additional information on risk factors.

The estrogen and heart disease conundrum has proven to be a quintessential paradigm supporting the *raison d'être* of rigorous clinical research. Biological plausibility notwithstanding, any inferences from observational studies need to be evaluated by well-designed prospective trials. In 2002 the Women's Health Initiative (WHI) findings¹² indicated that exogenous estrogen therapy (ET) did not prevent CVD. Indisputably, the WHI is the largest and best-designed hormone therapy (HT) study to date, yet its generalizability is somewhat limited to older women (mean age, 63) and an oral route of estrogen administration. A recent meta-analysis of 23 HT trials, including the WHI,¹³ showed a reduction of coronary heart disease (CHD) risk in younger women. This is consistent with the current SWAN report,⁹ in which estrogen secretory patterns that most

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resemble those of mid-reproductive-age women are associated with the lowest CVD risk. In other words, having a regular menstrual cycle may

be a marker for overall health. Additionally, in this context, having abundant endogenous estrogen does not appear to pose a cardiovascular risk.

Recommendations. Currently, a 5-year, multicenter, randomized clinical trial is under way to evaluate the effects of oral or transdermal ET on cardiovascular markers in newly postmenopausal women.¹⁴ Until the results of this trial are available, practitioners are well advised to utilize current recommendations for screening and treatment of CVD risk factors (Table 3, page 25).¹⁵

All patients should be counseled about prevention of CVD risk factors through smoking cessation programs, increased physical activity, eating a heart-healthy diet and maintaining a healthy weight. Patients at

Table 2. Relation of Cardiovascular Disease Risk Factors* to Reproductive Indices: Summary of Results from Matthews KA, et al, 2006.⁹

Hypothesis	Results	Conclusions
Evidence of luteal activity → ↓ CVD risk	Minimal association	Luteal activity in and of itself does not confer reduced CVD risk.
Longer ovulatory cycles → ↑ CVD risk	Significant association with 11 risk factors, only 2 after BMI adjustment	Excess body weight is a powerful predictor of both reproductive function and CVD risk.
Reproductively competent ovary ↓ CVD risk	Sex steroid urinary metabolites significantly associated with many hemostatic and metabolic risk factors, independent of age and BMI	This finding implies that slower reproductive aging may confer lower CVD risk.

BMI = body mass index, CVD = cardiovascular disease

*CVD risk factors measured: body composition parameters (waist circumference and BMI), blood pressure (systolic and diastolic), serum lipids and lipoproteins (total cholesterol, triglycerides, high-density lipoprotein-cholesterol, lipoprotein (a), apolipoprotein (b)), glucose metabolism markers (serum glucose and insulin) and hemostatic factors (fibrinogen, factor VII, tissue type plasminogen activator-antigen, plasminogen activator inhibitor type-1, C-reactive protein).

intermediate risk for CHD should be advised about and treated for hypertension, hypercholesterolemia and, for patients with diabetes, glycemic control. Additional treatment with aspirin, beta-blockers, and angiotensin-converting enzyme and angiotensin-receptor-blocker therapy is advised for high-risk patients. ■

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Table 3. Cardiovascular Risk Reduction in Women: American Heart Association/American College of Cardiology Consensus Committee Report: Class I Recommendations*

Risk Group Classification

Risk group	10-year absolute (CHD) risk	Examples
High	>20%	Established CHD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease
Intermediate	10%–20%	Subclinical CVD (eg, coronary calcification), metabolic syndrome, first-degree relative(s) with early-onset (age: <55 years in men and <65 years in women) atherosclerotic CVD
Lower	<10%	May include women with multiple risk factors, metabolic syndrome, or one or no risk factors

Practice Recommendations for Risk Reduction

Recommendation	Lower (<10% risk)	Intermediate (10%–20% risk)	High (>20% risk)
Smoking cessation	✓	✓	✓
Physical activity	✓	✓	✓
Heart-healthy diet	✓	✓	✓
Weight maintenance/reduction	✓	✓	✓
Treatment of individual CVD risk factors, as indicated	✓		
Blood pressure control		✓	✓
Lipid control		✓	✓
Aspirin therapy			✓
Beta-blocker therapy			✓
ACE inhibitor/ARB therapy			✓
Glycemic control in diabetics			✓

CHD = coronary heart disease, CVD = cardiovascular disease, ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker

*Modified from Mosca L, Appel LJ, Benjamin EJ, et al, 2004.¹⁵

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