Can Hysterectomy Be Considered a Risk Factor for Cardiovascular Disease?

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In this issue of Circulation, Howard and colleagues present a study on the risk of cardiovascular disease (CVD) by hysterectomy status using data from the Women’s Health Initiative Observational Study. The purpose of this editorial is to put their work and its findings into context by reviewing the literature both on the epidemiology of hysterectomy, as well as on menopause, sex hormones, and blood loss, and their impact on the risk of CVD.

Context

Hysterectomy is the most common nonobstetrical surgical procedure performed on women in the United States. In 2001, an estimated 649,000 hysterectomies were performed in the United States. Because most of the patients undergoing this procedure are between 25 and 54 years old, they live with the potential consequences of the procedure for many years. Thus, if hysterectomy is an independent risk factor for disease, then its attributable risk could be large even if the relative risk is small. This is especially true for CVD risk, a major cause of death among women.

Hysterectomy and Exposure to Sex Hormones

Howard et al state, as part of the rationale for their study, that hysterectomy reduces a woman’s exposure to endogenous hormones that are produced by the uterus and ovaries, especially when hysterectomy is performed significantly before the age at which natural menopause would have occurred. On the other hand, hysterectomy without concomitant bilateral oophorectomy usually is thought to preserve the hormonal milieu of the patient. Their thesis would therefore apply only to the estimated 50% of women who undergo bilateral oophorectomy at the time of hysterectomy.

To fully appreciate the intricacies of these associations, we need to understand some definitions related to menopause. The internationally recognized definition of natural menopause is the permanent cessation of menstruation, declared retrospectively after 12 consecutive months without menses with no apparent cause. Surgical menopause is the cessation of menses resulting from surgical removal of the uterus, leaving one or more ovaries, or the removal of both ovaries, with or without removal of the uterus. Thus, surgical menopause is also defined by a lack of menstruation, but there are 2 different causes for termination of bleeding. In many epidemiological studies, surgical menopause is treated as a single entity. Some researchers use the term induced menopause, the cessation of menstruation resulting from removal of both ovaries, to further delineate women who have functioning ovaries from those who do not.

The majority of studies to date that have investigated the effect of surgical menopause on CVD risk have found that disease risk is associated specifically with bilateral oophorectomy when it is performed significantly earlier than the average age of natural menopause. This confirms the theory that CVD risk may be modified by changes in exposure to endogenous sex hormones. Most research has not identified increased CVD risk among women who have undergone hysterectomy without simultaneous bilateral oophorectomy. Furthermore, the Nurses Health Study demonstrated that an increased risk of CVD incidence associated with induced menopause was eliminated if hormone replacement therapy was used after surgery, again supporting the theory that hormone exposure is the underlying causal agent of CVD risk changes resulting from surgical menopause.

Many studies have found no difference in hormone production after hysterectomy alone, as measured by age of menopause. These studies, however, are fraught with the methodological difficulties of measuring menopause and age of menopause, and so it is difficult to draw solid conclusions from them. There have been several reports of compromised ovarian function as measured by biochemical markers after hysterectomy, even when the ovaries have been preserved. If this is true, then hysterectomy could be considered an event that modifies the age of ovarian failure, at least for some women, although probably not to the same degree as does bilateral oophorectomy.

Following the logic that hysterectomy lowers the age of menopause necessitates a review of the association between natural menopause and CVD. Natural menopause has been
studied extensively as a potential risk factor for chronic disease, although most notably for osteoporosis.\textsuperscript{14–16} Women develop coronary heart disease $\approx$ 10 years later than do men, and some researchers have postulated that the reason for this is that endogenous sex hormones reduce the risk of heart disease for women until menopause, when hormone levels drop precipitously. Early menopause, that is, menopause occurring significantly earlier than the average of 48 to 52 years of age, also has been implicated in early mortality,\textsuperscript{17} again possibly indicating that a shorter exposure to endogenous hormones is a risk factor for a number of chronic diseases. Most of the recent large epidemiological studies of the relationship of natural menopause to CVD have found no significant association, especially when adequate control for age and smoking was performed.\textsuperscript{9}

Knowledge of the mechanisms that help explain menopause as a risk factor for CVD generally derive from studies investigating the effect of exogenous hormone use after menopause.\textsuperscript{16} These studies have found that exogenous hormones inhibit plaque formation, improve vascular flow, and improve lipid profiles.\textsuperscript{15,16} Unlike the earlier case-control and cohort studies, clinical trials of exogenous hormone use in women after menopause have found either unchanged or increased risk of heart disease morbidity and mortality rather than the expected decreased risk.\textsuperscript{18,19} It is not yet clear how these findings should be interpreted in regard to the effect that endogenous hormones have on heart disease risk among premenopausal women.

**Hysterectomy and Body Iron Stores**

Another mechanism by which hysterectomy could be associated with CVD is through its effect on body iron stores, a possibility alluded to by Howard et al. This theory, postulated to explain the difference in CVD mortality by sex, is that body iron stores are positively related to coronary heart disease (CHD) risk.\textsuperscript{20} Because premenopausal women have lower levels of body iron stores because of menstrual blood loss, under this hypothesis they would therefore have lower CHD morbidity and mortality. The theory implicates hysterectomy, not loss of ovarian function, as the CHD risk factor and thus all women who have had a hysterectomy would be equally at increased risk for disease regardless of ovarian surgery, as long as hysterectomy is performed significantly earlier than the age of natural menopause.

Although this proposed association between iron stores and CHD is biologically plausible, most epidemiological studies have failed to find the hypothesized association.\textsuperscript{20} This is true regardless of the measure used to quantify body iron stores, the cut point(s) used to define low and high iron stores, and the outcome studied. No study, however, has explored the association between iron stores and CHD among women by either age of menopause or type of menopause.

**Hysterectomy as a Marker for CVD Risk**

Another reason Howard and colleagues have studied hysterectomy in relation to CVD risk is that women who have had a hysterectomy may have a different CVD risk profile than other women.\textsuperscript{1} This reasoning implies that hysterectomy is a marker for CVD risk. A body of literature suggests that at least some variables associated with the use of hysterectomy are also factors that increase the risk for CVD morbidity and mortality.\textsuperscript{4} Most of the known factors that are associated with hysterectomy, such as reproductive history and socioeconomic status, are easily ascertained. If, however, there are other factors that determine CVD risk measured by hysterectomy that are less easily ascertained, then this knowledge may be useful to the general practitioner as a quick and easy way to identify patients at risk.

**Results**

Howard et al.\textsuperscript{1} present 2 conclusions from their analysis of the Women’s Health Initiative Observational Study. The first is that women who have had a hysterectomy tend to have a worse CVD risk profile than do other women. This study is probably the first to have sufficient power and an extensive-enough data collection to investigate these associations. Variables such as diabetes, cholesterol, and family history of CHD have previously not been investigated in relation to menopause type, and so the results are noteworthy. Only small differences between the hysterectomy-only group versus the hysterectomy-with-bilateral-oophorectomy group were noted, so that hysterectomy was found to be the marker for increased risk. The study could not, unfortunately, look at the directionality of these associations.

The second finding is that there was no independent association between hysterectomy and CVD after controlling for other major CVD risk factors. It would appear that a difference in CVD risk profile exists between women who undergo hysterectomy and those who do not, and this difference is responsible for an increased risk of incident CVD. Even when the outcome of interest was limited to CHD, a disease hypothesized to be more directly associated with estrogen exposure and iron stores, the association appeared to be between the known CHD risk factors and CHD, with no independent risk attributed to hysterectomy.

We could question whether hysterectomy changed the risk profiles of the women in this study because the study subjects were selected in some cases decades after the procedure had been performed. Previous research, however, has found no evidence that hysterectomy changes CVD risk factors such as blood pressure, lipid levels, or hemostatic factors.\textsuperscript{7} Although it is possible that some of the risk factors for hysterectomy may also influence CVD morbidity and mortality, there is no evidence that hysterectomy is a causal pathway for CVD risk.

Given the negative finding of this analysis, it appears that hysterectomy, with or without concomitant bilateral oophorectomy, is not a major risk factor for CVD. The analysis adds to the evidence against the hypothesis that changes in exposure to endogenous sex hormones or menopausal status influence the risk of CVD among premenopausal women. It also provides further evidence that body iron stores do not influence sex differences in CHD. In addition, because almost no residual risk was associated with hysterectomy status with or without bilateral oophorectomy, after controlling for major known CVD risk factors, hysterectomy does not appear to be a marker for future CVD. The CVD risk factors that differ by hysterectomy are fairly easily ascertained and are more specific in the identification of at-risk patients than is hyster-
ectomy status. These conclusions from this statistically powerful study help to bring closure to some of the existing theories of potential mechanisms for sex differences in CVD risk and underscore the need for new avenues of research.

Acknowledgment
The author thanks Dr Diane Makuc for her insightful editorial comments and suggestions in preparing this article.

References

Key Words: Editorials ■ women ■ menopause ■ risk factors ■ cardiovascular diseases
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Circulation. 2005;111:1456-1458
doi: 10.1161/01.CIR.0000161141.92300.F3
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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