Maturitas 104 (2017) 44–53

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

Gaps, limitations and new insights on endogenous estrogen and follicle stimulating hormone as related to risk of cardiovascular disease in women traversing the menopause: A narrative review

Samar R. El Khoudary*

Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, PA, USA

ARTICLE INFO

Keywords:
Endogenous sex hormones
Menopause
Cardiovascular disease
Hormone therapy
Estrogens
Follicle stimulating hormone

ABSTRACT

While it is known that estrogen protects heart health in women prior to menopause, its role after menopause and during the menopause transition is far less apparent. Previous reviews summarizing the literature on the impact of endogenous estrogen on risk of cardiovascular disease (CVD) have focused on postmenopausal women and have not come to a clear conclusion. No previous review has summarized the associations between follicle stimulating hormone (FSH), a proxy measure of the menopause transition, and CVD risk. The main purpose of this narrative review is to highlight gaps and limitations in the literature on endogenous estrogen and FSH as related to CVD risk. Future directions are addressed in light of recent findings in the field. When studying the relationship of estrogen to cardiovascular risk, it is critical to separate endogenously produced estrogen from exogenously administered estrogen. Moreover, other reproductive hormones such as FSH should be assessed, since growing evidence suggests a potential contribution of this hormone. Evaluation of estrogen changes over time allows a separation of women based on their hormone trajectories. These individual trajectories correlate with subclinical CVD and thus indicate that it is much more important to observe a woman over time rather than ascribe risk to a single determination at a single time point. As women progress through menopause and the ovary stops producing estradiol, the nature of the relationship between estrogens and subclinical CVD markers also appears to undergo a switch. Studies are needed to examine the midlife course of endogenous estradiol, FSH and CVD risk. These studies should also consider other hormones, including androgens, with an eye towards helping women modify their cardiovascular risk in midlife, when prevention is most likely possible.

1. Introduction

While it is recognized that estrogen protects heart health in women prior to menopause, its role after menopause and during the menopause transition is far less apparent. Previous reviews summarizing literature on the impact of endogenous estrogen on risk of cardiovascular disease (CVD) mainly focused on postmenopausal women and could not come to a clear conclusion. Findings on associations between follicle stimulating hormone (FSH), a proxy measure of the menopause transition, and CVD risk have never been evaluated. The main purpose of this narrative review is to highlight gaps and limitations in the existing literature on endogenous estrogen and FSH as related to CVD risk in light of recent findings from longitudinal studies of the menopause transition. Future directions are also addressed. The reported findings are mainly relevant to women who traverse menopause at a normal age for menopause. Women with premature/early menopause have other considerations that are not covered in this narrative review. Additionally, associations between changes in testosterone (T) and sex hormone binding globulin (SHBG) over the menopause transition, and CVD risk is beyond the scope of this work.

2. Methods

PubMed search engine was utilized to identify relevant articles on endogenous sex hormones and CVD risk in women transitioning through menopause. Key words included: estrogens, estradiol, cardiovascular disease, atherosclerosis, and women. “Follicle stimulating hormone” was not included as a key word since this would limit the ability to identify important articles on estrogens; adding “follicle stimulating hormone” to the search criteria resulted in narrowing the search results significantly. Instead; articles assessed estrogens were also reviewed for relevant results on FSH. Additionally; the word “menopause” was not included as a key word since the main focus of this narrative review is to evaluate studies assessed women at different

* Corresponding author.
E-mail address: elkhoudarys@edc.pitt.edu.

http://dx.doi.org/10.1016/j.maturitas.2017.08.003
Received 5 June 2017; Received in revised form 3 August 2017; Accepted 4 August 2017

stages of the menopause transition; and using the word "menopause" would narrow our search findings to studies exclusive to postmenopausal women. Search was limited to humans and English-language articles published till September 2016. Additional references were identified from reference lists in the resulting publications and review articles of interest. In total 240 articles were retrieved of which 26 were included in this review. Since this is a narrative review; a broader framework for understanding and contextualizing the limitations in the existing literature on associations between endogenous estradiol and CVD risk was utilized. Considerable background was also provided to give wide scope of the issue in the context of novel statistical methodology used to capture the dynamic changes in sex hormones across the midlife span; the period of life between 40 and 60 which encompasses the perimenopause stage.

3. Cardiovascular disease risk in women

Irrespective of the 25.3% decline in death rates due to CVD between 2004 and 2014 in USA, the burden of CVD is still high according to the American Heart Association 2017 statistics [1]. Yet in 2014, 1 of every 3 deaths was attributed to CVD with 36% of those deaths occurred before the age of 75 years, an age that is younger than the average life expectancy of 78.7 years [1]. CVD is the number 1 killer for women, a fact of which only 56% of women are aware [2]. Women's CVD risk increases at midlife [3], a time period coincident with the menopause transition. The accumulation of several adverse changes in sex hormones, body fat distribution, lipid/lipoprotein profile, metabolic syndrome severity/components and vascular remodeling [4–13] over the menopause transition could contribute to CVD development later in life. Interestingly, low levels of major CVD risk factors (e.g. blood pressure, total cholesterol, glucose, and smoking) at midlife were found to be associated with overall survival and morbidity free survival to $\geq$85 years of age [14]. Therefore, the midlife stage could be a critical window for optimizing CVD health and initiating early preventions.

3.1. Hormones and the heart, an endless controversy

Explaining the dramatic increase in CVD risk after menopause has been a challenging research question to many scientists and researchers for many years. It has been hypothesized that women are protected by their female sex hormones, particularly estrogens, up until menopause, when their estrogen levels decline. This hypothesis has been supported by several evidence including: the lag of coronary heart disease (CHD) incidence in women behind men by 10 years [15], and the uncommon presence of CVD before menopause, but more common among young women with premature menopause or bilateral oophorectomy [16]. A decline/loss of ovarian hormones after menopause is associated with worse CVD risk factors as reported in many epidemiological studies [17–24]. As reviewed elsewhere in more detail [25], two consistent notions can be gleaned from these studies: (1) women lacking endogenous estradiol have a higher CVD risk than women having normal ovarian function, and (2) postmenopausal women on hormone therapy (HT) have lower incidence and prevalence of CVD. Surprisingly, the reported cardio-protective effects from the observational epidemiological studies were not supported by several major randomized clinical trials [26–28], Table 1. Healthy user bias, implies participants who choose to receive one preventive therapy also seek other preventive services or partake in other healthy behaviors [29], has been widely proposed as a potential explanation for the protective effect of HT reported in many observational studies. Additionally, several criticisms have been made to explain the null/negative findings from clinical trials [30–32], Table 1. One central critique was that women were old (average age ranged from 63 to 66.7 years) to benefit from HT therapy (compared to women usually enrolled in observational studies). This thought led to what is currently known as the "timing hypothesis". The timing hypothesis implies that estrogen therapy could prevent CVD only if started early enough, within 5–10 years of the final menstrual period (FMP), assuming that estrogen therapy could cause CVD in older women who already have atherosclerosis (e.g. vulnerable plaque). In line with the timing hypothesis, secondary analyses from the Women's Health Initiative (WHI) trial showed that in women aged 50–59 years without prior use of HT at baseline the global index (which included stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture, and death) was significantly better in those on estrogen alone compared with women on placebo. Moreover, for estrogen alone compared to placebo, women aged 50–59 years had 19 *fewer* events per 10,000 person years, while women aged 70–79 years had 51 *more* adverse events, per 10,000 person years [33]. However, early reports from WHI did not show significant interactions with age or time since menopause [34,35]. Results from the Danish Osteoporosis Prevention Study (DOPS), an open label, randomized controlled trial in recently postmenopausal women, concluded that women receiving HT early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke [36]. While these results add to the literature which support that HT use is unlikely to be harmful if initiated early, major critiques were also raised [37,38], Table 1. Many other efforts have been conducted to test the timing hypothesis, including a meta-analysis of 39,049 women enrolled in 23 different clinical trials and followed for 191,340 patient-years. Results from this analysis showed that HT reduces CAD events in younger postmenopausal women (with mean time from menopause of less than 10 years) while it increases, then decreases risk over time in older women [39].

Since CAD event rates, the main outcome used in most clinical trials, are very low in young postmenopausal women, two recent clinical trials, KEEPS (Kronos Early Estrogen Prevention Study) [40] and ELITE (Early Versus Late Intervention Trial with Estrogen) [41], were designed to evaluate HT effects in recently postmenopausal women using intermediate CVD outcomes that could be detected in this young age group (e.g. subclinical measures of atherosclerosis), Table 1. The KEEPS trial did not find significant associations between HT and progression of atherosclerosis, despite improvement in some CVD risk factors [40]. Irrespective of the null findings from the KEEPS, KEEPS proved that HT use in early postmenopausal women is not associated with serious atherosclerotic progression over 4 years of use. On the other hand, the ELITE study showed that oral estradiol therapy was associated with less progression of carotid intima-media thickness (cIMT) than placebo when therapy was initiated within 6 years of the final menstrual period (FMP) but not when estradiol were administered at 10 or more years after menopause [41]. Irrespective of the cardio-protective effects on the progression of cIMT reported from the ELITE trial, the relevance of these recent results to CAD events remains unclear [42], Table 1. Obviously, much more still needs to be done to get a better understanding of the possible cardio-protective effects of HT. Until the existing controversy gets resolved, there is not enough support to clearly justify using postmenopausal HT for the purpose of preventing CVD events even in young postmenopausal women [43,44]. The take home message is that timing of initiation and characteristics of recipient of HT are critical factors to be considered when prescribing HT for postmenopausal women.

3.2. Exogenous estrogens do not have the same cardiovascular impact as endogenous estrogens

The controversies between results from studies assessed endogenously produced estrogens and those assessed exogenously administered estrogens in relation to CVD risk strongly emphasize that endogenous and exogenous estrogens are different and should be evaluated separately. Exogenously administered estrogens' effects on the cardiovascular system may be considerably modified by the hormonal component of the used HT preparation (opposing vs. facilitating