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Estrogen deprivation and cardiovascular disease risk in primary ovarian insufficiency

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Objective: To evaluate the association between estrogen (E) exposure and deficiency and cardiovascular disease (CVD) risk among women with primary ovarian insufficiency (POI).
Design: Cross-sectional study conducted between 1996 and 2016.
Setting: Tertiary referral centers.
Patient(s): A total of 385 women with POI, defined by amenorrhea and FSH levels $\geq$40 IU/L before 40 years of age, were recruited.
Intervention(s): None.
Main Outcome Measure(s): Women underwent a standardized intake questionnaire including data on menstrual cyclicity. Lifetime E exposure and E-free period were assessed. Serum was analyzed for endocrine and CVD profiles. The Framingham 30-year risk of CVD was calculated.
Result(s): Lifetime E exposure (mean $\pm$ SD) was 19.3 $\pm$ 7.0 years, E-free period was 3.1 $\pm$ 4.1 years, and age at screening was 34.8 $\pm$ 7.4 years. In multivariate models E-free interval associated positively with estimated risk of hard and general CVD events (β 0.18 [95% confidence interval 0.08, 0.29]; 0.20 [0.05, 0.35], respectively), and lifetime E exposure associated negatively with estimated risk of hard and general CVD events (−0.15 [−0.24, −0.05]; −0.16 [−0.29, −0.03], respectively), as well as low density lipoprotein cholesterol (−0.03 [−0.06, 0.00]) and non–high density lipoprotein cholesterol (−0.04 [−0.07, 0.00]).
Conclusion(s): Prolonged E deprivation is associated with an increased estimated risk of CVD, whereas prolonged E exposure is associated with a reduced estimated risk. These results support the policy of early and continued use of E replacement therapy in women with POI.
Clinical Trial Registration Number: NCT0230904. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Cardiovascular disease, estrogen, hormone replacement therapy, primary ovarian insufficiency

Cardiovascular disease (CVD) is the leading cause of death in women (1). Risk of CVD increases with age, and among women the menopausal transition is associated with an additional age-independent increase in risk of CVD (2, 3). Furthermore, women with early menopause (before the age of 45 years) have been found to exhibit an increased risk for and death from coronary heart disease, death from CVD, and a 12% higher risk of all-cause mortality compared with women with menopause after the age of 45 years (3).

Primary ovarian insufficiency (POI) is a rare disorder that could be considered the most severe form of early menopause. This disorder is characterized by diminished gonadal steroid production, absent or irregular menses, and postmenopausal levels of FSH above 40 IU/L before 40 years of age (4). Women with POI are believed to suffer from several long-term health complications, including increased risk

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for osteoporosis, fractures, depression, anxiety, and cognitive decline (5–7). These women also seem to be at increased risk of developing ischemic heart disease (hazard ratio 1.69) and total CVD (hazard ratio 1.61) (7–13) compared with healthy controls. At present, however, very few longitudinal studies with adequate sample sizes have evaluated the long-term health consequences of POI, limiting our understanding of disease risk in these women.

Elevated risk of CVD among women with POI is believed to be primarily due to estrogen (E) deficiency (14). Data supporting this claim are largely based on observational studies with naturally postmenopausal women and women with surgically induced menopause, in whom hormone therapy (HT) has been shown to reduce risk of CVD (15–17). Consequently, HT is commonly advised and prescribed to women with POI. However, this advice is not always followed, which may result in prolonged E-free periods and increased CVD risk (18). Overall there are surprisingly few data among women with POI to support the generally accepted paradigm that prolonged E deprivation results in increased risk of CVD.

We thus sought to assess the relationship between E status, E replacement therapy, and risk of CVD among a large cohort of well-phenotyped women with POI.

MATERIALS AND METHODS

Subjects

A cross-sectional analysis of a large prospective cohort study (the cycle disturbances, oligomenorrhea and amenorrhea [COLA] trial) on menstrual cycle disturbances was completed. Women were recruited at the University Medical Center, Utrecht, Erasmus Medical Center, Rotterdam, and VU Medical Center, Amsterdam between 1996 and 2016. Women were screened according to a standardized protocol that consisted of reproductive and medical history, anthropometric evaluations, transvaginal ultrasound, and an extensive fasting endocrine and metabolic laboratory evaluation. The screening procedures have been described in detail elsewhere (19). Study procedures were conducted with approval of the local institutional ethics review board, institutional review board number 12–645. The study was registered on www.clinicaltrials.gov (trial number NCT0230904). All participants provided written informed consent.

Primary ovarian insufficiency was assigned if women had a history of at least 3 months of amenorrhea as well as a serum FSH level of 40 IU/L or more before the age of 40 years (4). After diagnosis of POI was established, women underwent extensive screening for disease etiology. Serum was screened for autoimmunity (anti-thyroid peroxidase, anti-parietal cell, anti-thyrotropin receptor, anti-adrenal autoantibodies). Anti-thyroid peroxidase and thyrotropin receptor antibodies were measured by ELISA, and anti-parietal cell as well as anti-adrenal antibodies were detected by immunofluorescence. Karyotyping and DNA testing for fragile X permutation (FRAXA) was also done.

Menstrual Cycle and Hormone Exposure Characteristics

As part of the extensive baseline screening, recruited women were assessed for menstrual cycle and hormone exposure characteristics. Specifically, patients were interviewed for assessment of age at menarche, when menses ceased, and any climacteric symptoms around the time of menstrual cycle changes. Women were also asked to report any history of oral contraceptive or other forms of hormonal contraceptive use (OCP), as well as HT use. The period these medications were used was also recorded. On the basis of these reports the time taking HT and time taking OCP was calculated as any time between last menstruation and screening date when a woman used HT or OCPs, respectively. From these values an "E-free interval" was calculated as the time between the reported last menses to the screening date, minus any period of HT or OCP use during the period between last menses and screening. Furthermore "lifetime E exposure" was calculated by adding the time from menarche to last menstruation to any period of HT or OCP use that occurred after last menstruation (Supplemental Fig. 1, available online).

Endocrine and Metabolic Assessment

Baseline data were collected on body mass index (BMI), systolic and diastolic blood pressure, smoking history, and current medications. Blood samples were analyzed for FSH, LH, E_2, T, DHEA, sex hormone–binding globulin, androstenedione, insulin, glucose, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) was calculated with the use of the Friedewald formula: LDL-C = TC − HDL-C − (TG/5) (20). Non-HDL-C was calculated by subtracting HDL-C from TC. All biochemical parameters were assessed in fasting serum. Assays used to analyze samples have been described in detail elsewhere (21, 22).

CVD Risk Calculation

Risk of CVD was calculated for each woman using the Framingham 30-year CVD risk estimate (23). As reported by Pencina et al., risk of CVD is calculated for each woman according to gender, age, systolic blood pressure, use of antihypertensive medication, smoking, diabetes mellitus history, total cholesterol, and HDL-C. Furthermore, this group reported a simplified model using BMI instead of lipid measurements, which produces comparable 30-year risk of CVD. The simplified model was used for those women missing lipid data. The 30-year risk equation was developed using patients aged 20–59 years with a maximum duration of follow-up of 35 years. The equation generates a percent risk of developing "hard" CVD outcomes, including coronary death, myocardial infarction, fatal and nonfatal stroke, as well as "general" CVD outcomes, including coronary death, myocardial infarction, fatal and nonfatal stroke, coronary insufficiency, angina pectoris, transient ischemic attack, intermittent claudication, or congestive heart failure. Furthermore it generates an optimal percent risk of "hard" and "general" events given a woman's