Elevated basal FSH in normal cycling women is associated with unfavourable lipid levels and increased cardiovascular risk

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BACKGROUND: Cardiovascular disease is the leading cause of death in women, with most deaths occurring after menopause. It had been assumed that lack of estrogen is a leading contributing factor to cardiovascular disease in women. Recent trials, however, using hormone replacement therapy to treat cardiovascular disease in women have not affirmed the cardiovascular benefits ascribed to this regimen. Ovarian function declines slowly over the decades approaching the menopause as evidenced by declining fertility, rising serum FSH, falling inhibin, yet normal estradiol levels. We investigated the relationship between basal FSH and an established major risk factor for cardiovascular disease.

METHODS AND RESULTS: We obtained cycle day 3 serum FSH levels and fasting lipoprotein profiles on 40 women between the ages of 29 and 49 years, with normal menstrual cycles and who were not using hormonal medications or statins. Premenopausal women with an FSH level > 7 IU/l had significantly elevated total cholesterol (P = 0.009) and LDL (P = 0.019) compared with those with FSH < 7 IU/l. This difference was independent of age. Neither HDL nor triglyceride levels differed between the two groups.

CONCLUSIONS: Decreased functional ovarian reserve, as approximated by serum day 3 FSH levels, correlates with known cardiovascular risk factors. Declining ovarian function prior to estrogen deficiency may be a cardiac risk factor. The premenopausal ovary may be a source of cardioprotective substance other than estradiol. We hypothesize that factors other than 17β-estradiol, but related to ovarian function, might contribute to cardiovascular risk.

Key words: cardiovascular disease/cholesterol/FSH/lipids/ovary

Introduction

Cardiovascular disease is the leading cause of death in women, accounting for ~400 000 deaths in women annually in the USA, with almost all occurring in postmenopausal women (Wild, 1998). It had been assumed that this increased risk was entirely due to estrogen deficiency after menopause; however, more recent evidence suggests that there is not an abrupt increase in cardiovascular disease at the time of menopause (Barrett-Connor, 1997). The role of estrogen in atherosclerosis is still incompletely understood.

Estrogen may provide cardiovascular protection through direct vascular effects, increasing arterial vasodilatation and increasing perfusion, and by intrinsic antioxidant properties. Estrogen also has a favourable effect on lipid metabolism. Estrogen use leads to higher levels of high-density lipoprotein (HDL) cholesterol and lower levels of total cholesterol and low-density lipoprotein (LDL) cholesterol (The Writing Group for the PEPI Trial 1995; Grodstein et al., 1997). The postmenopausal period has been associated with decreased HDL and elevated LDL cholesterols. These atherogenic lipid changes are risk factors for cardiovascular disease (Stamler et al., 2000). While estrogen clearly modifies cardiovascular risk, atherosclerotic lesions likely originate prior to the onset of menopause (Barrett-Connor, 1997; de Aloysio et al., 1999). Recent prospective randomized trials using estrogen in an attempt to treat cardiovascular disease have not affirmed the expected benefits of estrogen (Hulley et al., 1998; Grady et al., 2002; Rossouw et al., 2002). Factors other than estrogen but related to ovarian function may influence lipoprotein levels and cardiovascular risk.

Menopause occurs at an average age of 51 years, (range: 44–59). Ovarian function declines before the menopause, as evidenced by shortening menstrual cycles, more frequent anovulatory cycles, and increased menstrual irregularity in the 4–5 years before menopause. Prior to menstrual irregularity and endocrine-related symptoms, there are subtle changes in hormone production, including reduced inhibin secretion and rising serum FSH levels (Klein and Soules, 1998). Women with regular menstrual cycles continue to have normal circulating concentrations of estradiol and progesterone after the age of 40 years and the onset of the monotropic FSH rise (Lee et al., 1988; Reame et al., 1996). In normal menstruating...
women, ovarian follicular dysfunction occurs as early as age 35, some 15 or more years before endocrine deficiency ensues.

The onset of declining ovarian reserve is highly variable. Basal FSH concentration on menstrual cycle day 3 has been a useful biomarker to estimate ovarian reserve; it is easily measurable, minimally invasive, inexpensive, and has a good predictive value. Day 3 FSH concentrations have been documented to increase from baseline in perimenopausal women (Bopp and Seifer, 1998). Numerous studies in assisted reproductive technology (ART) have demonstrated that, even in women with normal basal FSH, higher day 3 FSH is an indirect marker of declining ovarian reserve, as implied by poor ovarian response to ovulation induction (Pellicer et al., 1998) and higher cycle cancellation rate due to inadequate response to gonadotrophin therapy (Creus et al., 2000). There is no agreement as to what level of FSH marks the onset of ovarian decline; however, there is evidence of poor response to ovarian stimulation at day 3 FSH levels of as low as 7 IU/l (Pellicer et al., 1998; Seifer et al., 1999).

During the reproductive years, women are relatively protected from cardiovascular disease. Estrogen promotes a favourable lipid profile and may provide cardioprotective vascular effects. Additionally other factors associated with normal ovarian function may impact lipids and cardiovascular risk. Lipid changes in the premenopausal period, and hence an increased risk for atherogenesis, may take place when initial ovarian dysfunction begins prior to overt symptoms of estrogen deficiency. We examined the correlation between cycle day 3 FSH levels as a measure of ovarian reserve and lipid profiles in normally cycling women. Possible association between ovarian dysfunction and lipid levels could lead to earlier recognition of risk factors for cardiovascular disease.

**Subjects and methods**

We conducted a cross-sectional study of consecutive, healthy, regularly cycling women between the ages of 25 and 55 who presented as new patients to a gynecology clinic at Yale-New Haven Hospital. We obtained approval from our institutional review board for this study. From January 2000 to January 2001, 47 women consented to participation in the study. Menopause was defined as amenorrhea for at least 1 year. Only women with normal cycles, defined as menstrual cycles that occurred at regular intervals every 21 to 35 days, and without symptoms of ensuing menopause were included. Other exclusion criteria included women with known cardiovascular disease or hyperlipidaemia, defined as total cholesterol \( \geq 6.21 \text{ mmol/l} \) or LDL \( \geq 4.13 \text{ mmol/l} \); women in the past 1 year taking medications known to alter lipoprotein profiles, including hormones, in the form of HRT or hormonal contraceptives; women with an abnormal thyroid-stimulating hormone (TSH); and women who had undergone hysterectomy with or without oophorectomy. We excluded seven women from further analysis based on these criteria.

For the 40 remaining subjects, we obtained cycle day 3 serum FSH levels and fasting lipid profiles. We recorded their age, parity, height, weight, blood pressure, prior oral contraceptive pill (OCP) use, tobacco use, and history of hypertension or diabetes; these factors are known to affect cardiovascular risk (Berenson et al., 1998; Grundy et al., 1999). We performed unpaired Student \( t \)-tests to determine if an elevated serum day 3 FSH level (FSH \( \geq 7 \text{ IU/l} \)) in premenopausal women is associated with significantly higher total cholesterol, higher LDL, or lower HDL levels. To determine that the effects of FSH were independent of age, linear regression analysis was performed using Sigma Stat (Jandel Scientific Software, SPSS, Chicago, IL, USA). Statistical significance for all tests was set at \( P < 0.05 \). 95% confidence interval (CI) was calculated for the mean cholesterol level in each group.

The quantitative measurement of FSH in serum was performed with the IMMULITE FSH (EURO/DPC Ltd.) immunometric assay. Our lipid laboratory used the standards of the Center for Disease Control to measure total cholesterol and HDL cholesterol levels. LDL cholesterol levels were estimated with the Friedewald equation.

**Results**

The age range of the 40 included patients was 29–49 years, with a mean age of 38 years. There was no significant difference between the mean ages of the women with day 3 FSH \( <7 \text{ IU/l} \) and day 3 FSH \( \geq 7 \text{ IU/l} \). There were also no statistically significant differences between the groups in parity, body mass index (BMI), prior OCP use, blood pressure, hypertension, diabetes, or tobacco use. Estradiol levels were higher \( (P < 0.05) \) in women with FSH \( \geq 7 \text{ IU/l} \) (Table I).

When compared with premenopausal women with day 3 FSH \( <7 \text{ IU/l} \), premenopausal women with day 3 FSH \( \geq 7 \text{ IU/l} \) had significantly elevated serum total cholesterol [4.93 mmol/l (95% CI 4.88–4.98) versus 4.38 mmol/l (95% CI 4.31–4.45), \( P = 0.009 \)]. Similarly, premenopausal women with day 3 serum FSH \( \geq 7 \text{ IU/l} \) had significantly elevated LDL levels [3.05 mmol/l (95% CI 2.99–3.11) versus 2.52 mmol/l (95% CI 2.45–2.59), \( P = 0.019 \)]. In contrast, serum HDL levels did not differ significantly between the two groups (1.35 mmol/l versus 1.41 mmol/l) (Table II). Although there was no statistical difference in age between groups, FSH and cholesterol are both known to increase with age. To ensure that the effect of FSH on cholesterol was independent of the effect of age, linear regression analysis was performed. Linear regression analysis demonstrated the FSH levels correlated with cholesterol level and was independent of age \( (P = 0.03) \).

| Table I. Comparison of characteristics known to affect cardiac risk between women with day 3 serum FSH \( <7 \text{ IU/l} \) and women with day 3 serum FSH \( \geq 7 \text{ IU/l} \) |
|-----------------|-----------------|-----------------|
| **FSH <7 IU/l** | **FSH \( \geq 7 \text{ IU/l} \)** | **P-value** |
| Mean age (years) | 37 ± 1.9 | 39 ± 1.0 | NS |
| Mean BMI (kg/m²) | 27.0 | 27.2 | NS |
| Multiparous | 39% (7/18) | 41% (9/22) | NS |
| Prior OCP use | 39% (7/18) | 14% (3/22) | NS |
| Mean blood pressure | 113/70 | 116/71 | NS |
| Hypertension | 6% (1/18) | 5% (1/22) | NS |
| Diabetes | 0% (0/18) | 5% (1/22) | NS |
| Tobacco use | 6% (1/18) | 9% (2/22) | NS |
| Mean estradiol (pg/ml) | 27 | 52 | \( P < 0.05 \) |
Table II. Comparison of total cholesterol, LDL, HDL, and triglyceride levels between women with day 3 serum FSH <7 IU/l (n = 18) and women with day 3 serum FSH ≥7 IU/l (n = 22).

<table>
<thead>
<tr>
<th></th>
<th>FSH &lt; 7 IU/l</th>
<th>FSH ≥ 7 IU/l</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.37 ± 0.16</td>
<td>4.92 ± 0.13</td>
<td>0.009</td>
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<tr>
<td>LDL (mmol/l)</td>
<td>2.51 ± 0.16</td>
<td>3.06 ± 0.15</td>
<td>0.019</td>
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<tr>
<td>HDL (mmol/l)</td>
<td>1.35</td>
<td>1.41</td>
<td>0.49</td>
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<tr>
<td>Triglyceride (mmol/l)</td>
<td>2.54</td>
<td>2.62</td>
<td>0.87</td>
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Discussion

Cardiovascular disease is the single largest killer of American women, accounting for up to 50% of deaths each year (1998). Elevated total cholesterol and LDL levels have been associated with increased risk of cardiovascular disease (Grundy et al., 1999). Even in young adults, there is a continuous, graded relationship of baseline serum cholesterol level to long-term risk of cardiovascular disease and mortality (Stamler et al., 2000). Previous reports have shown that total and LDL cholesterol increase and HDL cholesterol decline among premenopausal women who cease menstruating at least 1 year relative to age-matched premenopausal women who continue menstruating (Matthews et al., 1989). We investigated the relationship between declining ovarian function and lipid levels in normally cycling women.

In ART the use of FSH measurements has been established as a marker of diminished ovarian reserve. Basal day 3 FSH level is a predictor of both pregnancy and treatment cycle cancellation rates (Scott et al., 1989; Toner et al., 1991). Women identified with diminished ovarian reserve, based on their poor response to gonadotrophin stimulation for ovulation induction or assisted reproduction, demonstrate higher serum FSH levels than controls, despite having FSH values within the normal range (Pellicer et al., 1998; Seifer et al., 1999; Creus et al., 2000). Diminished response and subtle ovarian dysfunction has been reported beginning with an FSH ≥7 IU/l (Pellicer et al., 1998; Seifer et al., 1999). Based on these studies, we set FSH of 7 IU/l as the threshold value for a sensitive marker of early ovarian dysfunction.

We demonstrate that in premenopausal women, a day 3 FSH ≥7 IU/l is associated with significant elevations in total cholesterol and LDL levels. Elevated serum FSH level in premenopausal women is associated with an unfavourable lipid profile, and therefore diminishing ovarian reserve in the years prior to menopause is predictive of an increased risk of cardiovascular disease in premenopausal women. The risk is not simply attributable to declining estrogen levels, as estradiol levels are relatively high in the perimenopausal period (Santoro et al., 1998). Similarly, HRT has failed to treat atherosclerosis in postmenopausal women. Relative androgen excess has also been associated with increased cardiovascular risk, producing unwanted effects on the cholesterol-lipoprotein profile (Wild, 1998). The period of time when estrogen levels begin to decline before the menopause has been described as a time of relative androgen excess (American Heart Association, 1998). However, our patients were normally cycling and did not have diminished estradiol levels. There are likely other as yet unidentified ovarian products, including other steroid hormones, cytokines and growth factors, which may be involved in mediating cardiovascular risk. Identification of potentially cardiovascular protective molecules of ovarian origin may explain the paradox of cardioprotection prior to menopause but lack of effective treatment with estrogen.

Ovarian decline and its sequelae should be viewed as a continuum rather than an abrupt event at the time of menopause. Beyond implications for fertility, evaluating ovarian reserve may provide another means of identifying women at increased cardiovascular risk in their premenopausal years. Prior to estrogen loss, declining ovarian function may contribute to cardiovascular risk (Grodinste et al., 1997).

References


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