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Mother's menopausal age is associated with her daughter's early follicular phase urinary follicle-stimulating hormone level

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Abstract

Objective: Early follicular phase follicle-stimulating hormone (FSH), a marker of ovarian reserve, has been used to predict time to menopause. A mother's age at menopause is related to her daughter's age at menopause, possibly because of genetic factors. In this study we sought to determine the relationship between maternal age at menopause and early follicular phase FSH of premenopausal daughters.

Design: The Uterine Fibroid Study enrolled women randomly selected from a prepaid health plan, collected questionnaire data, and obtained early follicular phase urine samples for a subset of participants. For this secondary analysis, premenopausal women between the ages of 35 and 46 years, who provided a urine sample on cycle day 2, 3, 4, or 5 and their mother's age at natural menopause (n = 182) were selected from the original cohort. Initially bivariate analysis and subsequently regression modeling were performed to assess the independent relationship between maternal age at menopause and urinary creatinine-corrected FSH.

Results: Unadjusted analyses and those adjusting for age (mean ± SD, 40.5 ± 3.2 y), smoking status (16% current smokers), and body mass index (26.8 ± 6.9 kg/m^2) showed a significant association between maternal age at menopause and daughter's urinary FSH level ($P < 0.04$). Women whose mothers experienced earlier menopause had higher urinary FSH levels.

Conclusions: The significantly increased FSH values among women whose mothers experienced early menopause is consistent with previously reported associations between mother's and daughter's age of menopause. FSH, a marker of ovarian reserve, is influenced by both genetic and environmental factors. Future epidemiologic studies on FSH should include collection of information on maternal age at menopause.

Key Words: Follicle-stimulating hormone – Menopause – Maternal age at menopause.

Reproductive aging of women is the natural progression through stages of puberty, fertility, subfertility, the menopausal transition, and finally menopause.[1] Women progress through these reproductive stages because of a decline in both the quantity and quality of ovarian oocytes and follicles. In the aging ovary, fewer follicles result in reduced follicular production of the hormone inhibin B, leading to diminished suppression of the anterior pituitary, increased follicle-stimulating hormone (FSH) production, and higher serum FSH levels during the early follicular phase of the menstrual cycle. Accordingly, early follicular phase serum FSH levels rise as the number of remaining oocytes declines.

On the basis of the hormonal changes observed with ovarian aging, serum FSH levels have been used as an indirect marker of reproductive potential. FSH levels are predictive of fecundity with fertility treatment.[2] Levels seem to rise as a woman goes through the menopausal transition from menstrual regularity to irregularity to amenorrhea.[3] In addition, FSH values seem to correlate with time to menopause in women between the ages of 40 and 49,[4] and extreme FSH levels (>20 IU/L) predict menopause (positive predictive value: 73%).[5] Urinary FSH levels are highly correlated with serum values ($r = 0.75$-0.88) and act similarly as a marker of ovarian aging.[6,7]

Women's age at menopause may vary owing to differences in the size of the oocyte pool at birth or differences in the rate of oocyte loss.[8] Previous studies have shown that both genetic and environmental factors determine the age at which women will enter menopause.[9,10] Maternal menopausal age seems to be a strong predictor of age at menopause.[11-13] The mechanism by which a mother's age at menopause determines the daughter's age at menopause is not known.

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If we assume that women destined to undergo early menopause will have a smaller oocyte pool, early follicular phase FSH should be higher in this group of women than in women destined to go through menopause later. On the basis of this assumption, FSH values should be higher in women whose mothers had an early menopausal age than in women with mothers who had a later menopausal age. In this study we sought to test this hypothesis by determining the relationship between maternal age at menopause and early follicular phase FSH among late reproductive age women.

METHODS

This study is a secondary analysis of data from the National Institute of Environmental Health Sciences Uterine Fibroids Study, which was designed to (1) measure prevalence of fibroids by screening a representative group of women and (2) identify risk factors for the condition. A detailed description of the study design has been published previously.[14] In summary, 35- to 49-year-old women were selected randomly from computerized membership records of a prepaid health plan in Washington, DC. Health plan members were eligible if they could be contacted by telephone and their records confirmed, and if they spoke English.

Demographic information, reproductive status, medical history, and social history were obtained from participants (N = 1,430) using a combination of a self-administered questionnaire and telephone interview. The take-home, self-administered questionnaire included questions about the cause of the mother's menopause (natural or surgical) and age at which it occurred, allowing respondents to possibly query their mothers. Of the 1,237 women who completed the questionnaire, 62% provided information about their mother's type and age of menopause.

The first 638 of the 1,243 premenopausal participants were asked to collect first morning urine samples on the 2nd and 3rd days of their menstrual cycles. The samples were initially stored in the woman's refrigerator and then shipped within a day via overnight courier in a cold-storage pack to the study management site in North Carolina where equal aliquots from each day were pooled. The premenopausal women who did not collect menstrually timed urine samples were asked to bring a first morning urine specimen, collected on the day of their study clinic visit. Those participants who presented to the clinic without urine samples were asked to provide a spot urine sample, and their menstrual cycle day was recorded. Seven percent glycerol was added to all samples, and the samples were stored at −80°C to prevent loss of hormone activity.[15] In all, 927 women provided urine samples, but many of these were not early follicular phase specimens. Serum FSH values have been shown to be consistent between menstrual cycle days 2 and 5,[16,17] so we limited analysis to specimens from those days. There were a total of 467 women with urine samples from menstrual days 2 to 5; 383 of them were 46 years of age or younger. Of the 383 women, 344 (90%) provided 2-day pooled first morning urine samples, 31 (8%) provided single first morning urine samples, and 8 (2%) provided single spot urine samples.

Urinary FSH was assayed in duplicate using a modified commercial noncompetitive, two-site time-resolved immunofluorometric assay.[18] Creatinine was measured spectrophotometrically.[19] Endocrine values were divided by creatinine concentrations to adjust for urine dilution.[20] Within- and between-assay percent coefficients of variation were 3.1% and 1.1% for FSH and 2.2% and 4.2% for creatinine.

We limited analysis to participants who were age 46 or younger for two reasons. First, very few women in our sample had experienced natural menopause by age 46, so selection of premenopausal women would not bias our analysis. Second, previous studies have shown that FSH and age are highly associated for older women.[5,21] By restricting our analysis, any relationship between mother's age at menopause and FSH would not be as obscured by the strong association between FSH and age.

Mother's age at menopause was grouped into three categories: younger than 46 years, 46 to 49 years, and 50 years or older. If the daughter reported that her mother had surgical menopause before age 50, her age at menopause could not be categorized, but if the daughter reported her mother had surgical menopause and surgery occurred after age 50 (n = 17), mother's age at menopause was grouped in the 50 years and older category. Of the 383 women with FSH data, 239 (62%) provided information about their mother's type and age of menopause. The 57 women (24%) who reported that their mothers underwent surgical menopause before age 50 were excluded, leaving 182 women for analysis of the relationship between maternal age at menopause and daughter's urinary FSH.

Data analysis

Analysis of variance and linear regression were used to determine the unadjusted relationship between FSH and each of the following variables: maternal age at menopause, age, race, education, body mass index (BMI), parity by age 35, and smoking status. Subsequently a model was created to assess the independent relationship between maternal age at menopause and urinary FSH (after log transformation), adjusting for potential confounders. Independent variables were considered to be confounders if they changed the measure of association between maternal age at menopause and urinary FSH by more than 10%. Categorical variables (smoking status, race, and education) were modeled using indicator variables. Parity by age 35 was coded as a ranked categorical variable. Age, BMI, and cycle day were modeled as continuous variables. The final model included age, current smoking status (yes/no), and BMI as covariates. Urinary FSH values were estimated for each independent variable using analysis of covariance with covariates set to the mean. Significance of the relationship between each independent variable and urinary FSH was determined using a t test for continuous or dichotomous variables, F test for categorical variables, and a test of trend t test for ranked

variables. The robustness of the maternal age at menopause effect was evaluated by substituting the mean for each category (mean for those with natural menopause, 52.7 y, used for the maternal age at menopause category of ≥50 y).

RESULTS

We compared daughters with data on mother's age at menopause with those without data. Compared with daughters without data, those with data on mother's age at menopause were lighter in weight (mean BMI = 26.8 ± 6.9 vs 29.1 ± 8.1 kg/m^2, $P = 0.003$), better educated ($P = 0.01$), less likely to smoke (16% vs 24%, $P = 0.05$), more likely to be white (45% vs 32%, $P = 0.05$), and similar in age (40.5 ± 3.2 vs 40.9 ± 3.0 y, $P = 0.2$). The average FSH value of the daughters for whom we could not categorize mother's age at menopause (n = 201) was similar to that of the daughters for whom we could categorize mother's age at menopause (n = 182) (11.2 vs 11.1 mIU/mg creatinine, $P = 0.9$).

Early follicular phase FSH values ranged from 0.58 to 69.3 mIU/mg creatinine (mean, 11.1; median, 9.3). Unadjusted analyses showed that of the covariates, only smoking status was a statistically significant predictor of early follicular phase urinary FSH. Current smokers had higher early follicular phase urinary FSH values than current nonsmokers (14.5 ± 12.5 vs 10.5 ± 6.8 mIU/mg creatinine, $P = 0.03$). BMI was next most important but was not statistically significant ($P = 0.06$). As BMI increased, FSH values decreased. Values did not differ by age, day of collection (day 2, 3, 4, or 5) ($P = 0.7$), race, education level, or parity by age 35.

Table 1 shows the relationship between maternal age at menopause and participant urinary FSH level. Early maternal menopause was significantly associated with higher urinary FSH levels in their daughters ($P = 0.04$ for both unadjusted and age-adjusted analyses). The relationship was somewhat stronger with full covariate adjustment ($P = 0.01$). Substituting the categorical mean maternal age at menopause for each individual maternal age at menopause in the model confirmed the significance of the relationship ($P = 0.01$).

In the fully adjusted model, smoking and BMI were the only covariates significantly associated with FSH levels. Current smokers had significantly higher urinary FSH values than current nonsmokers (estimated urinary FSH: 12.0 vs 8.6 mIU/mg creatinine, $P < 0.02$), and obese women had lower urinary FSH values than women in the three lower categories of BMI (estimated urinary FSH: 7.1 vs 9.3, 9.6, and 11.4 mIU/mg creatinine, $P = 0.01$). We reexamined former smokers and number of cigarettes in the full model and found that current smokers had higher urinary FSH levels than both never smokers ($P = 0.04$) and former smokers ($P = 0.03$). There was no significant difference between the never and former smokers ($P = 0.6$). Urinary FSH levels did not differ by number of cigarettes smoked by current smokers ($P = 0.5$).

DISCUSSION

In this study we found that mother's age at menopause may help predict her daughter's urinary FSH value. A woman's smoking status and BMI were also important, with smoking being associated with higher FSH levels and excess weight being associated with lower FSH levels. These findings support the hypothesis that both genetic and environmental factors contribute to the FSH level and presumably to ovarian aging for which FSH is a biomarker.

Previous studies have shown that a woman's age at menopause is related to her mother's age at menopause.[11-13] This relationship may be attributable to genetics or common behaviors, such as tobacco use, dietary intake, and physical activities. A genetic hypothesis is supported by twin studies, which reveal a heritability for age at menopause of 63%.[22] Pedigree analyses have revealed a potential dominant pattern of inheritance of early menopause (menopause between ages 40 and 45) and premature ovarian failure (menopause before age 40) through maternal or paternal relatives.[23,24] One potential familial cause of early menopause and premature ovarian failure is an alteration in the *FMR1* gene. Mutation of the *FMR1* gene resulting from expansion of the CGG repeat to more than 200 copies leads to fragile X syndrome. Trinucleotide repeats of 50 to 200 in the *FMR1* gene are associated with premature ovarian failure.[25] The length of the trinucleotide repeat has been correlated with age at menopause.[26] Women with longer repeat sequences had earlier onset of menopause, and women with shorter sequences had later onset.

Similarities in ages of mothers and daughters at menopause may also be attributed to common habits such as smoking, education level, and diet/exercise, resulting in similar BMI.[13] However, when we controlled for these

TABLE 1. *Relationship between maternal age at menopause and daughter's urinary FSH*

Maternal age at menopause	Number of women (n = 182)	Urinary FSH of daughter, mIU/mg creatinine		
		Mean ± SD	Age-adjusted mean (95% CI)[a]	Fully adjusted mean (95% CI)[a,b]
<46 y	25	13.4 ± 9.2	11.0 (8.5-14.3)	11.7 (9.0-15.2)
46-49 y	23	12.5 ± 6.6	10.8 (8.2-14.1)	10.9 (8.3-14.2)
≥50 y	134	10.5 ± 8.0	8.5 (7.6-9.5)	8.4 (7.5-9.4)
P[c]		0.04	0.04	0.01

FSH, follicle-stimulating hormone.
[a]After back-transformation from log FSH.
[b]Adjusted for age, current smoking status (yes/no), and body mass index.
[c]Linear regression test of trend.

factors, the effect of maternal age of menopause on FSH was not reduced, suggesting that the impact of maternal timing of menopause could be largely due to genetic phenomena rather than to shared environment.

Environmental factors that predict age of menopause also seem to be associated with elevated FSH levels. Current smoking and unilateral oophorectomy both seem to result in earlier onset of menopause[27-29] and higher premenopausal FSH levels,[2,5,30,31] whereas moderate alcohol use and increases in BMI have been associated with delayed onset of menopause.[11,12,32] BMI has also been associated with lower premenopausal FSH levels.[3,21] Although their mechanisms may differ, these factors may ultimately be linked to variations in the size or quality of the oocyte pool, presumably resulting in changes in serum FSH levels and in timing of the onset of menopause.

Our findings that mother's age at menopause predicts her daughter's FSH levels suggests that when FSH is used to monitor environmental impacts of potential reproductive toxicants on ovarian physiology, data on mother's age at menopause should be collected as a potential confounder or to improve precision of estimates. Future studies of younger women may determine whether the disparity in FSH between women with early and late maternal menopausal ages is due to a difference in the size of the initial oocyte pool or to a difference in the rate of oocyte depletion.

In our study of women between 35 and 46 years of age, we did not detect a significant relationship between urinary FSH and age. This finding may be due to several factors. First, this could be a chance result of our selection criteria. Second, the age range in our analysis was narrow. Third, we focused on younger women than have usually been described in the literature. The association between age and FSH may not be as strong in this age range as in older ages. The Third National Health and Nutrition Examination Survey showed that for the majority of women FSH remains relatively stable until age 45, when the values begin to rise.[5]

This study is limited by the fact that daughters provided the age at which their mothers went through menopause. The validity of this form of data collection has not been tested, and data have the potential for exposure misclassification owing to preferential recall by the perimenopausal women. Also, many mothers underwent hysterectomy before natural menopause and before age 50. We were unable to include them in the analysis, thus limiting the power of our study and increasing the probability that chance may explain the study findings. In addition, not all women are able to provide information on their mother's age at menopause (only 62% in our sample). Although they did not have significant differences in mean urinary FSH values, women who are able to provide information about their mother's age at menopause do differ from those who were not. Postmenopausal women were not included in our study; however, we limited the analysis to women aged 46 years and younger, an age group from which very few women were excluded because of early natural menopause. The study is strengthened by the collection and assessment of multiple covariates but may have benefited from collection and adjustment for other conditions thought to have an impact on FSH such as ovarian surgery.

CONCLUSIONS

In summary, maternal age at menopause is a significant predictor of urinary FSH, a marker of ovarian aging. Urinary FSH is an important independent predictor of ovarian aging independent of age. FSH is influenced by genetic and environmental factors, such as tobacco use and BMI. Researchers conducting epidemiologic studies using FSH as a marker of reproductive toxicity should consider collecting information on maternal age at menopause from study participants.

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