**Age at menarche: a predictor of diminished ovarian function?**

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**Objective:** To investigate whether age at menarche is associated with functional ovarian reserve (FOR) later in life.

**Design:** Retrospective cohort study.

**Setting:** Fertility center.

**Patient(s):** Five hundred and two infertile women.

**Intervention(s):** None.

**Main Outcome Measure(s):** Levels of menarcheal age, antimüllerian hormone (AMH), follicle-stimulating hormone (FSH), and functional ovarian reserve.

**Result(s):** The mean age of the patients was 38.9 ± 4.9 years, and their mean level of AMH was 1.4 ± 2.0 ng/mL and of FSH was 10.7 ± 6.1 mIU/mL. Their current age-specific diminished functional ovarian reserve (DFOR) was statistically significantly associated with early menarche, defined as age <13 years. Logistic regression analysis, adjusting for race, affirmed the higher likelihood of early age at menarche in infertile patients with DFOR. When women with DFOR were grouped into quartiles, early menarche (<25th percentile) was associated with statistically significantly higher DFOR risk than late menarche (>75th percentile).

**Conclusion(s):** This study demonstrates a statistically significant impact of age at menarche on DFOR risk later in life among infertile women. The occurrence of menarche may relate to follicular pool size and/or speed of follicle recruitment, which in turn is predictive of occurrence of DFOR later in life. (Fertil Steril® 2013;100:1039–43. ©2013 by American Society for Reproductive Medicine.)

**Key Words:** Antimüllerian hormone (AMH), follicle-stimulating hormone (FSH), diminished functional ovarian reserve, menarche, ovarian function

**Discussion:** You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/weghofera-menarche-diminishedovarian-function/
gene clusters of steroid hormone synthesis and metabolism were involved in premature ovarian failure and physiologic age at menopause. Genetic control of menopause is also suggested by high correlations of menopausal age between mothers and daughters (11).

Comparable associations also have been reported for age at menarche. Twin studies suggest significant concordance of age at menarche between monozygotic and dizygotic twins (12). Generational studies, in turn, have suggested that ethnicity and the mother’s and grandmother’s ages at menarche are highly predictive parameters for menarcheal age (13).

Though timing of menarche cannot be attributed to a single trigger, reactivation of gonadotropin-releasing hormone (GnRH) pulsatility has been assumed essential (14). The hypothesis that GnRH pulsatility is influenced by ovarian activity, and the observation that follicular recruitment peaks around menarche suggest a possible relationship between menarcheal age and a woman’s follicular pool (14, 15).

Studies on the impact of the fragile X mental retardation gene (FMR1) on ovarian function further support a genetic contribution to ovarian aging (16, 17). That this gene impacts ovarian aging has recently also been confirmed in a mouse model (18). In humans, CGG triple nucleotide repeats within premutation range (55–200 CGG repeats) on the FMR1 gene considerably increase a woman’s risk of premature ovarian failure (POF, also known as primary ovarian insufficiency) and the risk of neuropsychiatric diseases primarily in males (19). Within what are generally considered normal ranges, CGG repeats appear to correlate with different ovarian aging patterns (20, 21). We investigated whether menarcheal age is later in life statistically significantly associated with DFOR and possibly FMR1 genotypes.

MATERIALS AND METHODS

This study investigated 502 consecutive infertility patients who underwent fertility evaluations at the Center for Human Reproduction (CHR) in New York City between January 2005 and June 2012. All patients had a routine baseline evaluation; in addition to a detailed medical history, including age, race, body mass index (BMI), age at menarche, and indication for fertility treatments, they also received a baseline laboratory evaluation of ovarian function parameters. The latter included measurement of day 2–3 follicle-stimulating hormone (FSH) and estradiol levels, and measurement of AMH on random cycle days. Race was assigned according to National Institutes of Health guidelines (22). All relevant deidentified patient data were then entered into an electronic research database.

A diagnosis of DFOR was established, as previously reported, if a woman presented with an abnormally low age-specific antimüllerian hormone (AMH) level. These levels have been established as AMH levels below the 25th percentile at each 5-year age group, as previously reported in detail elsewhere (23).

The center’s initial routine workup also included genetic testing of CGG triple nucleotide repeats on the FMR1 gene, though such testing was performed with a special, additional “genetic” informed consent. Only a minority of women presented with CGG repeat numbers above 55 repeats, too few to draw conclusions on the timing of menarche. Moreover, some of those carriers decided to go into egg donation and did not undergo a complete fertility evaluation. Therefore, only women with so-called normal and gray-zone FMR1 genotypes of less than 55 CGG repeats were eligible for the analysis (19).

Among the eligible patients, the FMR1 genotypes and subgenotypes were further classified based on a previously reported normal range of 26 to 34 (median 30) CGG repeats: Normal (norm) was defined as both alleles within this normal range, heterozygous (het) was defined as one allele above (het-norm/high) or below (het-norm/low) the normal range, and the homozygous (hom) genotype was reflected as both alleles outside normal range (24). Hormone and genetic tests were performed by commercial assays, as previously reported elsewhere (25).

To assess the impact of age at menarche on later ovarian function parameters, the age at menarche was categorized as early or late based on a median age at menarche of 13.0 years: early <13 years, and late ≥13 years. The DFOR risk was then compared between women with early and late occurrence of menarche. Additionally, the study group was categorized into menarcheal age quartiles to compare the DFOR risk between the lowest and the highest quartiles.

The data we obtained only involved retrospective review of medical records and a deidentified research database. Patients at our center signed an informed consent at initial consultation, which allows for such reviews if the patient’s medical record remains confidential and her identity is protected. Specific genetic written consents were obtained for genetic analyses. These conditions were met in this case, allowing for expedited approval by the center’s institutional review board.

Statistical Analysis

Nonparametric tests—namely, the Mann-Whitney U test and chi-square tests—were performed to assess the potentially confounding factors of age-specific ovarian function, including BMI, race, and FMR1 genotypes/subgenotypes. Logistic regression was then used to examine the impact of age at menarche on ovarian function, categorized as the presence or lack of DFOR.

Statistical analyses were performed with SPSS 18.0 (SPSS, Inc.). The baseline characteristics of patients with early and late menarche were compared using t-tests. Continuous data are presented as mean ± standard deviation (SD). All tests were two-tailed, and P<.05 was considered statistically significant. In logistic regression models, alpha was set at 0.05 with regards to the individual contributions of predictor variables.

RESULTS

Table 1 summarizes the patient characteristics. The mean age for investigated patients was 38.9 ± 4.9 years. Three hundred and fifty women were Caucasians (69.7%), 91 were of Asian (18.1%) and 61 (12.2%) were of African descent. Two hundred
and sixty-six women (53.0%) had a norm FMR1 genotype, 182 tested het, 111 were het-norm/low and 71 het-norm/high (22.1% and 14.1%, respectively), and 54 (10.8%) were hom.

Indications for fertility treatment were tubal factor in 16.7%, diminished ovarian reserve in 62.5%, polycystic ovary syndrome (PCOS) in 7.2%, male factor infertility in 20.7%, and others in 5.2% (multiple entries possible); 95.4% of all participants had a history of female-factor infertility.

A statistically significant association between menarcheal age and DFOR, reflected in abnormal age-specific ovarian function testing, was observed. We found DFOR in 121 (62.7%) of 193 women with early menarche compared with 158 (51.1%) of 309 women with late menarche [chi-square (1, n = 502) = 6.43; P = .01; OR 1.6; 95% confidence interval (CI), 1.1, 2.3] (Fig. 1). Other possible confounding factors of menarcheal age such as race, BMI, and FMR1 genotypes and subgenotypes were not strongly associated with menarcheal age in the univariate analysis.

Statistically significant associations between FMR1 genotypes and ethnicity that had been previously observed elsewhere [25] were confirmed in our study group [chi-square (6, n = 502) = 18.67; P < .01]. Consequently, we performed a logistic regression analysis on age at menarche and FMR1 genotype, correcting for race. The results lacked a statistically significant association between menarcheal age and FMR1. However, race is also considered an influencing factor of age at menarche [26], so it was included in the logistic regression analysis, assessing the impact of age at menarche on DFOR. The results affirmed the higher likelihood of DFOR in women with early menarcheal age as compared with women with late menarcheal age [OR 1.6; 95% CI, 1.1, 2.3; P = .01] (Table 2).

When women with DFOR were grouped into quartiles: 43.4% entered menarche at age ≤ 12.0 years (<25th percentile), 27.6% entered menarche between the ages of 12.1 and 13.4 years (interquartile range), and 29.0% entered menarche at a later age (>75th percentile). Women with early menarche (<25th percentile) were more likely to have DFOR than the women who had experienced menarche at a later age (>75th percentile) [OR 1.6; 95% CI, 1.03, 2.42; P = .03]. The results also demonstrate an increased DFOR risk in women who undergo menarche earlier (<25th percentile) than the women falling into the interquartile range of 12.1–13.4 years at menarche [OR 1.6; 95% CI, 1.1, 2.5; P = .03]. Women entering menarche at a later age (>75th percentile) had similar odds of having DFOR as the women entering menarche in the interquartile range [OR 1.04; 95% CI, 0.6, 1.6; P = .87].

**DISCUSSION**

Our results with infertile women have demonstrated a statistically significant association between menarcheal age and DFOR later in life. Women who experienced menarche at a younger age were more likely to suffer from abnormally age-specific DFOR. These results were confirmed when the study group was divided into quartiles, pointing toward a relationship between follicular depletion, even already at very young ages, and reproductive life span.

Though the recently described likely presence of ovarian stem cells raises questions about the current concepts of

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**TABLE 1**

Patient characteristics of 502 infertile women undergoing fertility evaluations.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
</tr>
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<tbody>
<tr>
<td>Female age (y)</td>
<td>38.9 ± 4.9</td>
<td>39.7 (35.6, 42.6)</td>
</tr>
<tr>
<td>AMH (ng/mL)</td>
<td>1.4 ± 2.0</td>
<td>23.0 (20.8, 26.4)</td>
</tr>
<tr>
<td>Baseline FSH (mIU/mL)</td>
<td>10.7 ± 6.1</td>
<td>0.8 (0.2, 1.8)</td>
</tr>
<tr>
<td>Baseline estradiol (pg/mL)</td>
<td>52.2 ± 27.2</td>
<td>9.3 (7.0, 12.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.4 ± 5.0</td>
<td>47.7 (34.0, 63.4)</td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>12.9 ± 1.7</td>
<td>13.0 (12.0, 14.0)</td>
</tr>
</tbody>
</table>

**FIGURE 1**

Association between age at menarche and diminished ovarian function (DOR) risk in 502 infertile women.

ovarian senescence (27), a good number of studies in women with compromised follicle pools support a correlation between follicle pool size and reproductive lifespan (28–31). A retrospective analysis of risk factors for primary ovarian insufficiency/POF in 24,152 Japanese women demonstrated statistically significant associations between unilateral oophorectomy and POF (29). Chang et al. (28) reported comparable correlations between later menarche and a reduced risk of early menopause and POF.

To solely attribute ovarian function to follicle pool size, however, may be limiting, although our findings on increased DFOR risk in women with earlier menarche as well as generation analyses and genomewide association studies may support such an assumption. The current literature, indeed, convincingly demonstrates that a woman’s reproductive life span to a large extent is genetically predetermined (9, 13). Hefler et al. (32), for instance, show a statistically significant association between various polymorphisms and age at menopause. In contrast, data by Otero et al. (33) lack correlations between age at menarche and age at menopause.

Our group previously had demonstrated an association between FMR1 genotypes and subgenotypes and different ovarian aging patterns (17, 34). In a mouse model, Hoffman et al. (18) recently showed that the equivalent of a human premutation range FMR1-like genotype in comparison with wild-type mice demonstrated a variety of follicular abnormalities suggestive of premature ovarian aging, including accelerated follicle loss.

Thus, in this study we also examined the relationship between FMR1 genotypes and age at menarche. We did not find an association between FMR1 genotypes and age at menarche. These findings support the assumption that FMR1 genotypes and age at menarche reflect different contributing mechanisms to diminished ovarian function.

Our findings of a statistically significant association between age at menarche and subsequent DFOR risk later in life also suggest the question of whether such an association is attributable to ovarian follicular pool size, follicular depletion rate, or possibly a combination of both. Wallace and Kelsey (8), for instance, elegantly present mathematical models that support the assumption that women with larger follicle pools also demonstrate more extensive monthly follicle recruitment. They, however, also suggest a positive correlation between follicle pool size and menopausal age (8).

If, indeed, we assume an association among follicle pool size, follicular recruitment pace, age at menarche, and DFOR, we may also speculate that more extensive follicular recruitment leads to rapid follicular depletion and higher DFOR risk at middle ages—despite a larger initial ovarian follicle reserve.

Some POF studies have further supported the assumption that recruitment pace may be essential for the risk of diminished ovarian function: if follicle pool sizes and depletion rates are genetically influenced, as considerable scientific evidence suggests (9), higher POF rates after unilateral oophorectomy (29) likely reflect that depletion rates are pre-programmed and not adjusted under conditions of nonphysiologic changes in follicle pool size. Fleming et al. (15) go even further by demonstrating that follicular recruitment rates change in an age-dependent fashion: in healthy girls, follicular recruitment peaks around menarche and declines thereafter throughout the reproductive years. Consequently, AMH should experience peak levels when menarche is reached. AMH, however, follows a biphasic curve, with first peaks during puberty and, after a nadir, maximum levels reached around age 25. From then on, follicle pool size, recruitment rates, AMH levels, and fertility potential are highly correlated (15). These findings support our data on the predictive capacity of age at menarche for subsequent DFOR risk during later life.

The retrospective design of our study has to be seen as a limitation, though prospective evaluation of this hypothesis would require long-term observations and would thus appear to be difficult to perform. Additionally, a small minority of women (4.6%) underwent fertility evaluation due to male factor infertility. Compared with the study participants with female factor related infertility, this subgroup of patients presented with a comparable mean age at menarche; when excluded from the analysis, the differences observed in DFOR risk remained unchanged. However, this may be a limitation of the present study.

Our results suggest that the odds of developing DFOR at a more advanced age are increased for women who had an early rather than a late age at menarche. Because this study was performed in infertile women, the data presented are only

### Table 2

Regression analysis on confounding factors of diminished functional ovarian reserve (DFOR) in 502 infertile women.

<table>
<thead>
<tr>
<th>Race</th>
<th>P value*</th>
<th>β</th>
<th>Wald’s χ²</th>
<th>P value</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (reference)</td>
<td>.78</td>
<td></td>
<td>0.49</td>
<td>.78</td>
<td>0.87 (0.50, 1.51)</td>
<td></td>
</tr>
<tr>
<td>African</td>
<td>.01</td>
<td>0.48</td>
<td>6.39</td>
<td>.01</td>
<td>1.61 (1.11, 2.32)</td>
<td>1.61 (1.11, 2.32)</td>
</tr>
<tr>
<td>Asian</td>
<td>.01</td>
<td>0.48</td>
<td>6.39</td>
<td>.01</td>
<td>1.61 (1.11, 2.32)</td>
<td>1.61 (1.11, 2.32)</td>
</tr>
<tr>
<td>Age at menarche</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late onset (reference)</td>
<td>.01</td>
<td>0.48</td>
<td>6.39</td>
<td>.01</td>
<td>1.61 (1.11, 2.32)</td>
<td>1.61 (1.11, 2.32)</td>
</tr>
<tr>
<td>Early onset</td>
<td>.01</td>
<td>0.48</td>
<td>6.39</td>
<td>.01</td>
<td>1.61 (1.11, 2.32)</td>
<td>1.61 (1.11, 2.32)</td>
</tr>
</tbody>
</table>

Note: CI = Confidence interval; OR = odds ratio.

* Values are based on the chi-square test for categorical or dichotomous variables.
applicable to infertile women, but it appears likely that our outlined model of ovarian aging may be generally applicable.

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