Long-term Effects of Reproductive-Age Menstrual Cycle Patterns on Peri- and Postmenopausal Fracture Risk

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The authors examined the association between age at menarche, menstrual cycle characteristics between ages 28 and 32 years, and peri- and postmenopausal fracture risk in a cohort of 874 women who prospectively recorded menstrual cycle data for at least 5 years from their early 20s through their menopause. Fracture history was obtained with a self-administered questionnaire. The mean age of respondents at the time the questionnaire was completed was 73 years. Wrist fracture \( (n = 62) \) risk increased with increasing age at menarche (odds ratio 3.3, 95% confidence interval 1.7-6.2) for menarche age 21-24 years compared with 12-13 years) and increasing mean cycle length at age 28-32 (odds ratio 2.2, 95% confidence interval 1.0-4.9) for >30.5 days compared with 26.6-30.5 days). Similar results were seen in analyses of the combined wrist, hip, or vertebral fracture group \( (n = 92) \). These prospectively recorded menstrual diary data indicate that age at menarche and menstrual cycle patterns may have a long-term association with fracture risk, with effects lasting into the postmenopausal years. Am J Epidemiol 1997;145:804-9.

Osteoporosis is a significant public health problem, particularly among older women. A protective effect of estrogen replacement therapy on bone mineral density (BMD) and on fracture incidence has been clearly demonstrated (1, 2). Factors that may affect endogenous estrogen levels or metabolism (e.g., smoking, lean body mass) have also been associated with BMD in studies in pre- and in postmenopausal women (1, 3).

Low BMD in premenopausal women has been reported in association with amenorrhea or oligomenorrhea (4), particularly in relation to exercise (5, 6) and to eating disorders (7). Relatively little is known about the relation between menstrual cycle characteristics (cycle length, variability, and bleeding duration) and BMD or fracture risk in the general population of pre- or postmenopausal women.

A later age at menarche may result in a decreased estrogen exposure during the critical period of adolescent bone development (8, 9). Long cycles may reflect relatively low estrogen levels as they represent a larger proportion of time spent in the early part of the follicular phase during which estrogen (and progesterone) levels are very low (10). Our primary hypothesis was that relatively low levels of endogenous estrogen as characterized by long menstrual cycles and a late age at menarche would be associated with fracture risk and that this risk would extend beyond the reproductive years. We examined the association between cycle characteristics and fractures in a cohort of 874 women followed from approximately 1935 to 1990. These women prospectively recorded menstrual cycle data for 5 or more years from their early 20s through their menopause, providing the opportunity to examine these relations with little misclassification or disease-related recall bias.

**MATERIALS AND METHODS**

The menstrual cycle data for this analysis came from the Menstruation and Reproductive History Study begun in 1934 by Alan Treloar and colleagues at the University of Minnesota (11). Participants in this menstrual diary study recorded beginning and ending dates of bleeding periods on a calendar card covering successive 1-year periods. A questionnaire that included information about pregnancies, hormone use, surgery, and other medical conditions was also completed annually. Age at menarche was obtained at the time the participant first began recording menstrual cycle data.

Between 1934 and 1939, 1,807 women younger than 25 years (primarily college students) enrolled in
this study; 1,134 of them contributed 5 or more years of menstrual data. In 1989, a follow-up study of these 1,134 women was begun. Information necessary for tracing (i.e., name, date of birth, and last known address) was available for 997 women, and 943 (94.6 percent) were successfully located by 1991. Details of the tracing procedures have been described (12).

A self-administered questionnaire was completed by 874 respondents (716 study subjects and 158 proxies, most often a daughter or husband) between 1990 and 1991. The questionnaire contained questions about fracture history both before and after age 40, with specific questions about fractures of the ribs, hip, wrist, vertebra, leg, and arm. Data pertaining to fracture history were missing for 42 participants, and so the total sample available for this analysis was 832.

In 1995, the respondents who had indicated a history of a wrist, hip, or vertebral fracture after age 40 were contacted by phone to confirm this report and to obtain information about the age and circumstances surrounding the fracture. Of the 100 respondents who reported a wrist, hip, or vertebral fracture after age 40, 11 had indicated they did not want to be recontacted, six declined to participate in the telephone interview, and four could not be located. Of the 79 who were interviewed, 70 (89 percent) provided information that was in agreement with the previously collected fracture data. In 13 cases, the respondent who completed the telephone interview differed from the respondent who had completed the follow-up questionnaire (usually because of death or illness of the participant). As expected, agreement was less in these cases (62 and 94 percent agreement for different and same respondents, respectively). Fifty-three (67 percent) of the telephone respondents provided information on the specific age of the fracture.

Based on the information provided by the 79 telephone respondents, we determined that five fracture cases (two wrist, one hip, and two vertebral) had resulted from a severe trauma situation (e.g., automobile accident) and three occurred 4, 8, or 11 years before menopause. We excluded these from our defined fracture cases and compared the 62 wrist fracture respondents with the 770 without a history of a wrist fracture. Ninety-two respondents who reported a peri-

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We used the remaining cycles to compute summary measures (e.g., mean, standard deviation) for cycle length and bleeding duration for ages 28–32. Cycle length was calculated as the number of days from the start of one bleeding period through the day before the next recorded menses. Bleeding duration was calculated as the number of days from the start of one menstrual bleeding period through the last day of bleeding before an indication of the end of menses was recorded.

We used logistic regression to analyze the association between fracture risk, age at menarche, and cycle characteristics. We analyzed the menarche age and menstrual cycle data as categorical variables with the cut-points roughly corresponding to the top and bottom quintiles; we included age at time of questionnaire or at death as a covariate in these models.

The self-administered questionnaire included questions about the following several factors that were associated with menstrual cycle characteristics (13) or that have been associated with fracture risk: current height and weight at age 30 (which we used to calculate the body mass or Quetelet index (kg/m²)); usual consumption (cups per week) of milk, beer, wine, and liquor between ages 20 and 40; smoking history; and physical activity during ages 23–34, 35–49, and ≥50 years. Two questions about physical activity were asked for each age period (participation in vigorous sports such as jogging, swimming, tennis, dancing, and heavy physical activity at work), with response categories of less than once per week, once per week, or every day. Information on type of menopause, age at menopause, and use of estrogen replacement therapy was also collected in the questionnaire and was used to supplement the information from the prospectively collected menstrual diary data. These factors were examined as potential confounders in our analysis.
RESULTS

All of the study participants were white women of northern European ancestry, and the mean age of the subjects who were alive at follow-up was 73 years (range 63–81). There were 62 wrist, 18 hip, and 18 vertebral fractures among the 92 women included as fracture cases in this analysis, and the median age when these occurred was 64 years (range 45–77). Sixty-six percent of the fractures after age 40 for which we were able to obtain specific age information in the telephone interview occurred more than 10 years after menopause, 13 percent occurred 6–10 years after menopause, 9 percent occurred 1–5 years after menopause, and 11 percent occurred within the 2 years before menopause.

Mean age at menarche was 12.4 years (standard deviation (SD) 1.35) and ranged from 8 to 18 years. The mean cycle length was 29.0 days (SD 4.81), with approximately 1 percent of the values in the upper tail of the distribution (>44 days). Cycle variability (standard deviation) was also skewed, with a mean of 3.5 (SD 4.30) days. Mean bleeding duration was 5.3 (SD 0.97) days.

Twenty-six percent had a surgical menopause (defined as bilateral oophorectomy or a hysterectomy), and the mean ages at surgical and natural menopause were 45.0 and 50.4 years, respectively. Approximately 38 percent smoked during ages 28–32, and 31 percent did not drink alcohol. Between 16 and 18 percent reported either heavy physical activity or participation in vigorous sports during ages 23–34, 35–49, or ≥50, with concordance between these age groups ≥85 percent.

The association between menstrual cycle characteristics and wrist fracture risk is shown in table 1. Fracture risk increased among women who were older at menarche (adjusted odds ratio (OR) = 3.3 for menarche age ≥14 compared with 12–13 years). Fracture risk increased with increasing menstrual cycle length at age 28–32 (OR = 2.2 for mean cycle length >30.5 days compared with 26.6–30.5 days) and increasing bleeding duration (OR = 1.7 for >6.0 days compared with 4.7–6.0 days). Cycle variability (mean standard deviation of cycle length) was correlated with mean cycle length (r = 0.76 and 0.70, for the untransformed and log-transformed distributions, respectively) but was not independently associated with fracture risk. Inclusion of other potential confounders (menopause type, estrogen use, smoking, alcohol, physical activity, milk consumption, body mass index at age 30) did not change the risk estimates (data not shown).

In the separate analysis of the combined fracture group, we compared the 92 women who reported a peri- or postmenopausal wrist, hip, or vertebral fracture with the 740 women who did not report this type of fracture. The associations with menarche age and cycle length were similar to those observed in the wrist fracture analysis (ORs = 1.40 and 3.16 for menarche ages 8–11 and 14–18 years, respectively, and ORs =

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### Table 1. Relation between wrist fracture* risk and menstrual-related characteristics based on 1990–1991 self-administered questionnaire data for women followed from approximately 1935 to 1990 in the Menstruation and Reproductive History Study

<table>
<thead>
<tr>
<th>Average age at menarche (years)</th>
<th>No.</th>
<th>% with wrist fracture</th>
<th>Adj. OR†</th>
<th>95% CI (adj. OR)</th>
<th>Adjusted OR‡</th>
<th>95% CI (adj. OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8–11</td>
<td>11</td>
<td>5.8</td>
<td>1.04</td>
<td>0.52–2.08</td>
<td>1.25</td>
<td>0.61–2.57</td>
</tr>
<tr>
<td>12–13</td>
<td>12</td>
<td>5.7</td>
<td>1.0</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>14–18</td>
<td>14</td>
<td>14.5</td>
<td>2.75</td>
<td>1.52–4.99</td>
<td>3.29</td>
<td>1.73–6.23</td>
</tr>
<tr>
<td>Mean cycle length (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤26.5</td>
<td>25.7</td>
<td>4.5</td>
<td>0.65</td>
<td>0.29–1.44</td>
<td>0.60</td>
<td>0.26–1.38</td>
</tr>
<tr>
<td>&gt;26.5 – ≤30.5</td>
<td>28.3</td>
<td>6.7</td>
<td>1.0</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;30.5</td>
<td>32.8</td>
<td>11.5</td>
<td>1.83</td>
<td>0.99–3.39</td>
<td>2.23</td>
<td>1.02–4.89</td>
</tr>
<tr>
<td>Standard deviation of cycle length (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1.75</td>
<td>1.49</td>
<td>7.5</td>
<td>1.17</td>
<td>0.59–2.30</td>
<td>1.47</td>
<td>0.72–3.01</td>
</tr>
<tr>
<td>1.76–3.75</td>
<td>2.40</td>
<td>6.4</td>
<td>1.0</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;3.75</td>
<td>5.23</td>
<td>8.5</td>
<td>1.40</td>
<td>0.74–2.66</td>
<td>0.80</td>
<td>0.36–1.76</td>
</tr>
<tr>
<td>Mean bleeding duration (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4.6</td>
<td>4.1</td>
<td>2.9</td>
<td>0.36</td>
<td>0.14–0.94</td>
<td>0.37</td>
<td>0.14–0.97</td>
</tr>
<tr>
<td>4.7–6.0</td>
<td>5.2</td>
<td>7.3</td>
<td>1.0</td>
<td>1.0</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>6.5</td>
<td>11.6</td>
<td>1.68</td>
<td>0.91–3.10</td>
<td>1.66</td>
<td>0.89–3.13</td>
</tr>
</tbody>
</table>

* Total of 62 women with a peri- or postmenopausal wrist fracture compared with 770 without a wrist fracture.
† Adjusted for age at last contact or death.
‡ Adjusted for age at last contact or death and the other factors in the table (57 cases, 736 controls).
DISCUSSION

In our analysis of peri- and postmenopausal fracture risk, we observed an association between older age at menarche and wrist fractures and with the combined category of wrist, hip, or vertebral fractures. This supports the idea that there may be important long-term consequences of age at menarche on bone development and strength. Later menarche has been associated with lower bone mineral content or BMD at the wrist in perimenopausal women (14) and in postmenopausal women (mean age 71 years) (15), but no association was seen with calcaneus BMD (16). Previous studies of age at menarche and fracture risk have produced conflicting findings (16–18). In a case-control study of 102 hip and 154 wrist fractures, an increased risk was reported for menarche ≥13 compared with <13 years of age, but the confidence intervals were wide: For wrist fractures, OR = 1.35 (95 percent confidence interval (CI) 0.67–2.76); and for the combined fracture group (hip or wrist fracture), OR = 1.24 (95 percent CI 0.79–1.96) (17). Paganini-Hill et al. (18) reported a reduced risk in relation to hip fractures for menarche ages ≥14 compared with ≤13 years (relative risk = 0.72, 95 percent CI 0.55–0.93) in a prospective cohort study of 8,600 postmenopausal women (18).

We observed increased peri- and postmenopausal fracture risk in association with increased mean menstrual cycle length during ages 28–32. Including covariates that may be associated with menstrual cycle patterns (e.g., Quetelet index, physical activity, alcohol use) (13) did not change our results. This was seen even with relatively small differences in cycle length (e.g., from 26 to 33 days) and supports the hypothesis that even these small differences may be important. No association was seen between recalled cycle length and radial BMD in the study by Fox et al. (15), but menstrual cycle information retrospectively assessed in postmenopausal women may be subject to misclassification. No other studies have evaluated the risk of wrist fractures in relation to menstrual cycle length, but Paganini-Hill et al. (18) reported a reduced risk of hip fracture with longer menstrual cycles (as recalled by women at a median age of 73 years).

We did not observe an association between fracture risk and cycle variability as measured by the standard deviation of the cycle length. Highly variable cycle lengths (very long and very short cycles) may indicate anovulatory cycles, and this may reflect either hypoestrogenic or hyperestrogenic conditions (19). We could not differentiate between these possibilities using menstrual cycle records, so our results may reflect heterogeneity within the exposure classification.

Short bleeding duration was associated with a lower wrist fracture risk in our data. There have been no other studies of fracture risk and bleeding duration; however, in contrast to the protective effects we observed, Fox et al. (15) reported a lower radial BMD in relation to shorter bleeding. Shorter bleeding duration has been associated with greater body mass, increased physical activity (13, 20), and African-American ethnicity (21), each of which is associated with decreased fracture risk (1). Our study population was limited to white women, and controlling for physical activity and body mass using the retrospectively collected questionnaire data in our analysis did not change the association we observed between bleeding duration and fracture risk. We are not aware of other reports that would provide support for a relation between bleeding duration and measures of health risk associated with bone or other endocrine-related diseases. Other than the relation between dysfunctional uterine bleeding and endometrial prostaglandin activity (22), relatively little is known about physiologic influences on bleeding duration.

Wrist fractures were the most common fracture occurring in this cohort of women. This was expected given the age distribution (63–81 years at the time of data collection) and younger age at wrist compared with hip fracture (17, 23). It is possible that the associations between menstrual characteristics and fractures occurring in later years (≥80 years) could be diminished as other factors (i.e., comorbidity, balance) play a stronger role (24) or could be missed if previous fractures are a basis for exclusion from a study of later-age fractures.

The major strength of our study is that menstrual cycle characteristics are based on prospectively collected diary data in a large cohort of women. Age at menarche was collected at the time of entry into the study cohort, and the mean length of recall for this variable was 7.0 years. Oral contraceptives were not available until these women were older than 40. A specific definition of menstrual bleeding was not provided, so some variability in recording between women is likely. However, the likelihood of misclassification of these factors is considerably reduced compared with studies of postmenopausal women that rely on recalled menstrual cycle and age at menarche data (15, 18). On average, the errors introduced by nondifferential misclassification can be expected to attenuate estimates of association, but the magnitude
and direction of this effect in any one study cannot be assured.

We included information from proxy respondents so that women who had died could be included in the analysis. This reduces the extent to which censoring related to cycle characteristics and mortality or morbidity risk could have biased our results, although we anticipate that misclassification of fracture history and other risk factors would be more common in the proxy data. Our results from the analyses based only on self-respondents were similar to those reported for the full sample, indicating that little bias was introduced by including the proxy respondents in the analyses.

The agreement between the 1990 self-administered questionnaire and the 1995 telephone interview provides some sense of the reliability of the data for those who reported a wrist, hip, or vertebral fracture. However, we did not confirm these fracture histories by medical record review, so some misclassification may have occurred. In two studies of the accuracy of self-reported fractures, the false-positive rate of reported hip or wrist fracture was 0 percent among women ages 36–61 (25) and 8–11 percent among women 65 years and older (26). However, these reports concerned recent fractures, and the accuracy level of long-term recall can be expected to be lower. Underreporting fractures may also occur, with an estimated frequency of false-negative reports of wrist fracture among women of approximately 20 percent (27).

Our observations indicate that age at menarche and menstrual cycle patterns (cycle length and bleeding duration) during the reproductive years may have a long-term association with fracture risk, with effects lasting into the postmenopausal years. A clearer understanding of the relation between menstrual cycle patterns and postmenopausal fracture risk may help identify women at increased risk of osteoporotic fractures. These women may benefit from targeted prevention strategies. For example, the long-term (i.e., postmenopausal) effect of oral contraceptives among the subset of women who use them specifically because of long cycles or prolonged bleeding periods has not been evaluated. Additional research is needed to characterize the hormonal profiles of women with long and variable cycle lengths and the biologic significance of variability in bleeding duration.

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