MENSTRUAL AND REPRODUCTIVE CHARACTERISTICS AND AGE AT NATURAL MENOPAUSE

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Data from women who enrolled between 1935 and 1939 in a long-term prospective study of menstrual and reproductive health, in which menstrual cycles and other events were recorded as they occurred, were analyzed to examine factors associated with age at natural menopause. Analysis was restricted to 561 women who enrolled before age 25 years and recorded data through at least age 44 years. Women with a median cycle length that was less than 26 days at ages 20–35 years reached menopause 1.4 years earlier than those with cycles between 26 and 32 days. The difference in mean menopausal age between women with short cycle length (less than 26 days) and women with long cycle length (33 days or longer) was 2.2 years. Women who had ever been pregnant reached menopause slightly, but statistically significantly, later than women who had never been pregnant. Similarly, women who had ever had a live birth had a slightly later age at menopause compared with nulliparous women. A trend of later age at menopause with increasing parity was also observed. There was no association with age at menarche. Certain of these observations are consistent with proposed mechanisms of cessation of menstrual function.

menopause; menstrual cycle; parity

There is considerable uncertainty as to what factors affect the timing of menopause; this is despite recent advances in our understanding of hormone changes associated with menopause and in the treatments available to relieve menopausal symptoms. Factors that affect menopause timing may have important clinical implications because early menopause is associated with an increased risk of cardiovascular disease (1) and osteoporosis (2), whereas delayed menopause has been associated with increased risk of breast cancer (3) and endometrial cancer (4). These associations may result from a direct effect of menstrual function (or cessation of function) and re-

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Abbreviations: CI, confidence interval; OR, odds ratio.

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lated hormone changes or may be an indirect result of other factors, such as reproductive events, that are associated with age at menopause.

Numerous studies have investigated the effect of reproductive factors on age at menopause, but results are inconsistent or unconfirmed. Disparity in the findings of previous studies may have resulted from differences in the populations studied with respect to age range and health status or differences in definitions, methods of data collection, and analysis. Previous studies used retrospectively collected information on age at menopause and reproductive history, which may have been subject to biased or inaccurate recall (5, 6). At least one study examined menstrual characteristics in relation to age at menopause (7), but this study was based on recall of menstrual patterns.

We examined menstrual and reproductive factors and age at menopause using data from a prospective study of menstrual and reproductive health (8). We describe the relation between age at menopause and several reproductive factors that were routinely recorded by study participants at the time of occurrence. These factors include pregnancy-related events and menstrual cycle patterns during early adulthood.

MATERIALS AND METHODS

The Menstruation and Reproductive History Study is an ongoing project begun by Dr. Alan Treloar in 1934 at the University of Minnesota as a prospective study of menstrual cycle variability (8). A total of 3,962 women have enrolled in this study, primarily during two recruitment periods. Between 1935 and 1939, 1,997 college women enrolled. An additional 1,256 women were recruited during the period 1960–1964. A group of 709 daughters of participants as well as other volunteers were admitted at various times. Approximately 40 percent of the participants continue to provide data to the Tremin Trust Research Program, which currently manages the Menstruation and Reproductive History Study data base. The present analysis includes data collected through 1980.

At the time of enrollment, women completed a questionnaire covering age at menarche and previous menstrual history. Each participant then maintained a daily calendar card, recording menstrual flows by date of occurrence, as well as events that might have disrupted the menstrual cycle (e.g., pregnancy). Yearly questionnaires provided additional information about the use of exogenous hormones, pregnancy, surgery, and hospitalizations.

No attempt was made to identify reproductive events that occurred before a woman enrolled in the study or during a break in her history. To minimize misclassification of women by reproductive status and to restrict analysis to women at risk of natural menopause, we limited the present analysis to the 649 women who enrolled in the Menstruation and Reproductive History Study before age 25 years and who contributed data at least through age 44 years or menopause. Further restriction was made to women whose longest break in history was less than 2 years, excluding an additional 88 women, leaving 561 women remaining for analysis. Because some women might have pathologic conditions resulting in very early or very late menopause, analysis was restricted to the experience of women between ages 44 and 56 years. Nine women experienced menopause before age 44 years. Ten women who experienced menopause after age 56 years were included in the analysis until age 56 years and then censored. Of the 561 women in the analysis, 408 (73 percent) experienced natural menopause, 107 (19 percent) had surgical menopause, and 46 (8 percent) had no record of menopause as of 1980.

The analysis of menstrual cycle length and variability was restricted to cycles recorded between ages 20 and 35 years because these cycles are least likely to be affected by the variability of menses that occurs near menarche and menopause. A
total of 92,336 cycles were recorded during this age interval. Exclusions were made for cycles potentially affected by exogenous hormone use or recent pregnancy because these conditions are known to affect menstrual cycles. For live births and stillbirths, six cycles after delivery were excluded. For a reported spontaneous abortion, induced abortion, or ectopic pregnancy, three cycles after the event were excluded. Cycles in which exogenous hormones were used and three cycles after cessation of use of exogenous hormones were also excluded. These exclusions left 68,285 cycles available for analysis.

Median menstrual cycle length was used as a measure of central tendency for each woman, and cycle variability was assessed for each woman as the difference between the fifth and 75th percentiles of cycle length. The distribution of cycle lengths for the study sample includes a number of extremely long cycles that may represent such factors as unreported pregnancy loss or unreported breaks in recording of menses. The asymmetrical range, fifth to 75th, was chosen because it is insensitive to these long extremes of cycle length.

Logistic regression (9) was used to model the "odds" of natural menopause for each year of age over the interval 44–56 years, as related to the factors of interest. This approach is the discrete-time survival model proposed by Cox (10). Women who had surgical menopause were treated as censored observations and withdrawn from the analysis at the year of surgery. Summary odds ratios and 95 percent confidence intervals were generated from the regression coefficients and their standard errors produced by the logistic model. Adjusted analyses produced estimates for each variable controlling for the remaining variables. An odds ratio greater than 1.0 for women with a given risk factor indicates a greater risk of menopause at each age, i.e., an earlier age at menopause relative to women without that factor. An odds ratio less than 1.0 indicates later menopause. Mean age at natural menopause was calculated for each variable of interest using standard life table techniques.

**RESULTS**

Figure 1 shows the probability distribution for age at natural menopause based on the cumulative experience of all 561 women in the study sample. The distribution was estimated conditional on occurrence between ages 44 and 56 years, and correcting for surgical menopause as an independent competing risk. The estimated mean age at natural menopause is 50.5 years.

Table 1 presents the relation between menstrual factors and menopausal age. Menstrual cycle length between ages 20 and 35 years had a strong relation to age at natural menopause. At any given age, women who had a median cycle length of less than 26 days when they were age 20–35 years were more likely to reach menopause (odds ratio (OR) = 1.57, 95 percent confidence interval (CI) 1.03–2.39), i.e., they reached menopause earlier than women who had had a median cycle length of 26–32 days. A median cycle length of 33 days or longer was related to later menopause (OR = 0.74, 95 percent CI 0.46–1.19). Adjusting for the other variables had little effect on these results. Women who had a median cycle length of less than 26 days had menopause 1.4 years earlier, on average, than women who had a median cycle length of 26–32 days. The difference in mean menopausal age between women with short cycle length and women with long

TABLE 1

Menstrual factors and age at natural menopause, Menstruation and Reproductive History Study, 1935-1980

<table>
<thead>
<tr>
<th>Median cycle length (ages 20-35 years)</th>
<th>No.</th>
<th>OR (95% CI)*</th>
<th>Adjusted OR (95% CI)*</th>
<th>Mean age at natural menopause (years)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26 days</td>
<td>41</td>
<td>1.57 (1.03-2.39)</td>
<td>1.62 (1.06-2.47)§</td>
<td>49.2</td>
</tr>
<tr>
<td>26-32 days</td>
<td>428</td>
<td>1.00</td>
<td>1.00</td>
<td>50.6</td>
</tr>
<tr>
<td>≥33 days</td>
<td>38</td>
<td>0.74 (0.46-1.19)</td>
<td>0.74 (0.46-1.19)</td>
<td>51.4</td>
</tr>
</tbody>
</table>

Fifth to 75th percentile of cycle length (ages 20-35 years)

| <6 days                                | 318 | 1.00        | 1.00§                 | 50.5                                  |
| 6-8 days                               | 160 | 1.08 (0.85-1.38) | 1.10 (0.86-1.41)    | 50.4                                  |
| ≥9 days                                | 63  | 0.76 (0.53-1.09) | 0.75 (0.52-1.08)    | 51.9                                  |

Age at menarche (years)¶

| <12 years                              | 155 | 0.90 (0.69-1.18) | 0.88 (0.67-1.14)¶ | 50.5                                  |
| 12-14 years                            | 365 | 1.00        | 1.00¶               | 50.4                                  |
| ≥15 years                              | 38  | 0.97 (0.63-1.49) | 1.01 (0.65-1.56)¶ | 51.1                                  |

* OR, odds ratio; CI, confidence interval.
† Summary OR and 95% CI calculated using logistic regression to model the "odds" of natural menopause for each year of age over the interval 44-56 years.
‡ Calculated using standard life table techniques.
§ Adjusted for parity and age at menarche.
¶ Random fluctuations in these data can produce inconsistencies between the logistic model estimates and the nonparametric estimates of mean age at menopause, such as those seen here for age at menarche.
† Adjusted for parity and median cycle length at ages 20-35 years.

Cycle length was 2.2 years. This relation (unadjusted) is illustrated graphically in figure 2, which shows the estimated percent of women who are postmenopausal by age and median menstrual cycle length. The association between menstrual cycle length and age at menopause is modeled as a linear relation, such that each 1-day increase in median cycle length was estimated to contribute a 10 percent decrease in the odds of menopause (OR = 0.90, 95 percent CI 0.85-0.95).

Cycle length is known to decrease with increasing age (8). To be sure that the association between cycle length and menopause is not explained by age-related changes in cycle characteristics, we examined the association between menstrual cycle length at each of three ages (20-24 years, 25-29 years, and 30-34 years) and age at menopause. The association persisted for each of the three intervals examined. For example, odds ratios associated with short cycle length were 1.5, 1.3, and 1.7, respectively.

FIGURE 2. Percent postmenopausal by median menstrual cycle length at ages 20-35 years (Kaplan-Meier estimates), Menstruation and Reproductive History Study, 1935-1980.
A high degree of cycle variability (a difference of 9 or more days between the fifth and 75th percentiles for cycle length) between ages 20 and 35 years was associated with later age at menopause (OR = 0.76, 95 percent CI 0.53–1.09). This relation remained after adjustment for parity and age at menarche. However, when the joint effects of cycle length and cycle variability on age at menopause were examined, the relation between cycle variability and age at menopause was entirely explained by cycle length (adjusted OR = 1.16). Cycle length remained an important predictor of age at menopause even after controlling for variability (adjusted OR for short cycle length = 1.63). Adjusted for parity and cycle length, age at menarche was not associated with age at menopause.

Pregnancy-related variables had a modest effect on age at menopause (table 2). At any given age, women who had ever been pregnant were less likely to reach menopause than women who had never been pregnant.
pregnant (OR = 0.71, 95 percent CI 0.52-0.96). The estimated mean age at menopause for gravid women was 50.6 years compared with 50.1 years for nulligravid women. Similarly, women who had ever had a live birth had a later age at menopause compared with nulliparous women (OR = 0.75, 95 percent CI 0.56-1.01). A trend toward later menopausal age with increasing parity was observed, with mean age at menopause of 50.5, 50.7, and 51.0 years for women with 1 or 2, 3 or 4, and 5 or more live births, respectively, compared with 50.0 years for nulliparous women. Adjustment did not change these results. To address the concern that the association between high parity and later menopause may simply reflect a longer reproductive life, we restricted the analysis to women whose last birth occurred before age 40 years and found the same trend of later menopause with increasing parity. History of spontaneous abortion among gravid women was not associated with age at natural menopause.

Among parous women, those who had their first birth at age 30 years or older appeared to have a slightly earlier menopause (OR = 1.25, 95 percent CI 0.95-1.66), but there was no consistent trend with increasing age at first birth. Having ever breast-fed was not associated with age at menopause (OR = 0.88, 95 percent CI 0.66-1.16). Adjustment for parity, age at menarche, and median menstrual cycle length did not change these results.

**DISCUSSION**

We observed a strong association between the length of menstrual cycles during young adulthood and age at natural menopause. Short cycle length during this time was associated with earlier menopause, whereas long cycles were related to later menopause. Cycle variability was not associated with age at menopause after taking into account cycle length. We also observed an association of later age at menopause with both parity and gravidity. These observations are consistent with proposed mechanisms of cessation of menstrual function.

Few studies have examined the relation between menstrual cycle characteristics and menopause. Data from the Menstruation and Reproductive History Study were used by others (11-13) to examine the association between menstrual cycle characteristics during the perimenopausal interval and age at menopause. Women with late onset of menopause had longer and more variable cycles in the 2 years prior to menopause (12), but it is difficult to distinguish changes due to onset of the menopausal transition from changes that predispose to altered age at menopause. Stanford et al. (7) focused on menstrual cycles early in life, but data were retrospective and limited to self-reported regularity of cycles. They found that women who reported regular menstrual cycles before age 25 years or first live birth reached menopause almost 2 years earlier than those with irregular cycles during this time. To the extent that “regular” cycles reflect short cycle length and “irregular” cycles reflect a proportion of long cycles, this finding is consistent with our results. Stanford et al. (7) speculated that the association between irregular cycles and later age at menopause could reflect the association between anovulation and irregular cycles, which is compatible with the notion that menopause occurs after a certain degree of depletion of oocytes.

The lack of an association between age at menarche and age at menopause observed in our study is consistent with findings from most other studies (7, 14-17). Because age at menarche was ascertained at enrollment in the Menstruation and Reproductive History Study, and enrollment was generally only 5-10 years after onset of menses, there is less opportunity than in other studies for recall bias to influence reports.

Of the pregnancy-related variables, parity was the most consistently related to age at menopause. Women with five or more births had menopause approximately 1 year
later than nulliparous women. Several previous studies reported that parous women have menopause at a later age compared with nulliparous women (7, 14, 15, 18, 19), although others found no association (16, 20). Two of the positive studies (15, 19) report an association with parity only in women of upper socioeconomic status, and two found a trend with increasing parity (7, 19). Lower parity could potentially be an effect rather than a cause of early menopause. This explanation seems unlikely, however, because the actual difference observed in age at menopause is only about 1 year.

We did not observe a trend in age at menopause with increasing age at first birth, although women who had a first birth at age 30 years or older had a slightly earlier menopause than other women. Two other studies found no association between age at first birth and age at menopause (7, 21).

The use of hormones during the perimenopausal interval can make it difficult to assess age at menopause accurately because hormone use may artificially prolong apparent cyclic menstrual bleeding. To the extent that hormone use may be associated with cycle characteristics or other reproductive factors, it is important to determine if our observations could be explained by intervening hormone use. Restricting the study population to the 347 women who did not use exogenous hormones within 5 years of menopause or conclusion of follow-up did not appreciably alter the results.

Several of our observations are consistent with the theory that menopause occurs after sufficient depletion of oocytes, including the marked association of short (regular) cycles with early menopause and the later age at menopause among parous or gravid women (fewer cumulative cycles). On the other hand, early age at menarche, which has been shown to be related to early onset of ovulatory cycles (22), was not associated with earlier menopause. Breast feeding, which suppresses ovulation, might be expected to delay onset of menopause. We found no such association, but the available data on breast feeding were limited.

There may be a nonlinear relation between number of oocytes and age at menopause. Gosden (23) suggested that changes in oocyte number have little effect on the age of menopause until significant oocyte depletion is reached. A study that used an autopsy data base modeled the effect of varying oocyte number and rate of atresia on age at menopause. Atresia is the degeneration and resorption of an ovarian follicle before it reaches maturity. The study suggested that age at menopause is more sensitive to varying rates of atresia than to depletion of the absolute number of oocytes (24). The effect of alteration of the rate of atresia on age at menopause is difficult to determine in humans. In rats and mice, removal of the pituitary gland retards the rate of atresia (25–27), indicating that one or more pituitary hormones may be involved. Short menstrual cycle length may be directly associated with increased rates of follicular atresia, or more likely, certain aspects of the neuroendocrine system, in particular the pituitary gland, may influence both menstrual cycle length and the rate of atresia.

Data on exogenous factors that may influence age at menopause (either directly or indirectly) were not available. For example, because cigarette smoking data were not available and because previous reports show that cigarette smoking decreases the age of menopause by 1–2 years (20, 28, 29), we cannot be sure that confounding by smoking status does not explain our results.

Another potential limitation of this analysis relates to the generalizability of the findings. Women in the Menstruation and Reproductive History Study are college-educated, white volunteers who were self-selected for the long-term enrollment required for our analysis. The similarity of several of our results to those of previous studies is reassuring in this regard.

In conclusion, based on prospectively recorded data, menstrual cycle length early in reproductive life may be associated with...
subsequent age at menopause. Age at menopause may be a marker for hormonal status earlier in life, and hormonal status early in reproductive life could ultimately influence the risk of certain chronic diseases reported to be related to menopausal status.

REFERENCES