Long or Highly Irregular Menstrual Cycles as a Marker for Risk of Type 2 Diabetes Mellitus

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OBJECTIVE To prospectively assess risk of type 2 DM in women with a history of long or highly irregular menstrual cycles.

Participants A total of 101,073 women who had no prior history of DM and who reported their usual menstrual cycle pattern at age 18 to 22 years on the baseline (1989) questionnaire.

Main Outcome Measure Incident reports of DM, with follow-up through 1997, compared among women categorized by menstrual cycle length (5 categories).

RESULTS During 564,333 person-years of follow-up, there were 507 cases of type 2 DM. Compared with women with a usual cycle length of 26 to 31 days (referent category) at age 18 to 22 years, the relative risk (RR) of type 2 DM among women with a menstrual cycle length that was 40 days or more or was too irregular to estimate was 2.08 (95% CI, 1.62-2.66), adjusting for body mass index at age 18 years and several other potential confounding variables. The RR of type 2 DM associated with long or highly irregular menstrual cycles was greater in obese women, but was also increased in nonobese women (at body mass indexes at age 18 years of <25, 25-29, and $\geq$30 kg/m², RRs were 1.67 [95% CI, 1.14-2.45], 1.74 [95% CI, 1.07-2.82], and 3.86 [95% CI, 2.33-6.38], respectively).

Conclusion Women with long or highly irregular menstrual cycles have a significantly increased risk for developing type 2 DM that is not completely explained by obesity.
MENSTRUAL CYCLES AND TYPE 2 DIABETES MELLITUS

ity level, and personal history of DM and hypertension and associated treatment. Physical activity level was derived from estimation of the usual duration of participation each week in 8 common activities (walking, running, jogging, bicycling, calisthenics/aerobics, tennis, lap swimming, and other aerobic recreation). Information was also collected on usual menstrual cycle length at age 18 to 22 years (categorized as <21 days, 21-25 days, 26-31 days, 32-39 days, 40-50 days, >50 days, or too irregular to estimate) and usual cycle pattern at age 18 to 22 years, excluding time around pregnancies or when using oral contraceptives (very regular [within 3 days], regular, usually irregular, always irregular, no periods). At baseline, women were asked about a history of severe teenage acne and, in 1991, about a history of physician-diagnosed hirsutism. In 1993 and 1997, women were also asked about a history of infertility treatment with agents to induce ovulation. Weight was reassessed on each biennial questionnaire.

Women subsequently reporting a new diagnosis of DM were sent supplementary questionnaires asking about diagnosis, treatment, and history of ketoadiposis, to confirm the self-report and to distinguish type 1 from type 2 DM.

For this analysis, women were excluded for the following reasons: (1) did not respond to the question about menstrual cycle length, (2) had DM or were menopausal at baseline, and (3) diagnosis could not be confirmed by the supplementary questionnaire to be consistent with type 2 DM. We also excluded women who reported consistent oral contraceptive use during the years of self-described cycle characteristics (at least 10 months per year for each year between age 18 and 22 years). The distribution of person-time by category of usual menstrual cycle length at age 18 to 22 years was as follows: less than 21 days, 1.0%; 21 to 25 days, 10.0%; 26 to 31 days, 66.1%; 32 to 39 days, 15.3%; and 40 days or more or too irregular to estimate, 7.6%.

Validation Studies
Several studies have confirmed a high accuracy of self-report among women participating in this study or the NHS, a companion cohort comprising older nurses. Among a sample of 184 participants in the NHS, the correlation between reported and measured body weight was 0.96. Similarly, among a subset of NHS II participants, correlations between self-reported weight and height at age 18 years, and weight and height recorded on entry to nursing school, were 0.87 and 0.94, respectively. The validity of supplementary questionnaires to confirm and characterize DM type has also been validated in the NHS. Of a subset of 84 women whose supplementary questionnaire information was diagnostic of definite type 2 DM, 71 gave permission for medical record review; records were obtained for 62 of these women. On review by an endocrinologist blinded to the supplementary questionnaire information, the diagnosis of type 2 DM was confirmed by National Diabetes Data Group criteria in 61 (98%) of the 62 women.

Statistical Analysis
We calculated person-time for each participant from the date of return of the baseline questionnaire to the date of diagnosis of DM or June 1, 1997, whichever came first. We considered women reporting a usual menstrual cycle length of 26 to 31 days at age 18 to 22 years to be the referent group, and women reporting menstrual cycle lengths of 40 days or longer were considered oligomenorrheic. Relative risks (RRs) and 95% confidence intervals (CIs) for development of DM were estimated using pooled logistic regression, which approximates a Cox regression analysis. Covariates obtained from the baseline or subsequent questionnaires were used in multivariate analyses, including age (continuous), body mass index (BMI) at age 18 years or currently (6 categories), family history of DM in a first-degree relative (yes or no), physical activity level (5 categories of total MET [metabolic equivalent] expenditure), cigarette smoking (current, past, never), weight change (from BMI at age 18 years to current BMI), race, and use of oral contraceptives. These covariates were chosen based on recognized or potential associations between these factors and risk of DM. We also tested for effect modification by BMI and family history of DM by performing analyses stratified by these variables. Statistical analysis was performed using SAS statistical software (SAS Institute Inc, Cary, NC).

RESULTS
Baseline characteristics of the study cohort as a function of menstrual cycle length are shown in Table 1. Compared with women with a normal menstrual cycle length (26-31 days), women with short cycles (<21 days) appeared more likely to be nonwhite, to have a family history of DM in a first-degree relative, to be current smokers, and to have a history of oral contraceptive use at study entry in 1989; women with long (≥40 days) or highly irregular cycles had higher BMI both at age 18 years and at study entry and greater weight gain from the age of 18 years. Women with either short or long cycles were more likely than women with a cycle length of 26 to 31 days to report severe teenage acne, physician-diagnosed hirsutism, ovulatory infertility, and a history of gestational DM; histories of hirsutism, ovulatory infertility, and gestational DM were particularly prevalent in the women with long or highly irregular cycles.

During 564333 person-years of follow-up, we documented 507 cases of definite type 2 DM. Compared with women whose menstrual cycle length at age 18 to 22 years was 26 to 31 days, the RR for type 2 DM was modestly but not significantly elevated among women with a cycle length of less than 21 days both in age-adjusted analyses and after adjustment for BMI at age 18 years, physical activity level in 1989, smoking status in 1989, family history of DM in a first-degree relative, and history of oral contraceptive use (multivariate RR, 1.50; 95% CI, 0.70-3.19). Women with usual menstrual cycle lengths of 21 to 25 days or 32 to 39 days had subsequent risks for DM very com-
Menstrual cycles and type 2 DM appeared slightly stronger among women whose BMI at age 18 years was greater than 30 kg/m² than among less obese women. However, even among women with a BMI of less than 25 kg/m², a history of long or highly irregular cycles was a significant predictor of subsequent type 2 DM. Short cycles were associated with an increased risk for DM in women with a family history of DM in a first-degree relative, but not in women without this history. However, a history of long or highly irregular cycles was associated with an increased risk for DM regardless of family history of DM (Table 3).

To minimize the likelihood of screening bias among women with irregular menstrual cycles, we did an analysis including as cases only the 395 women reporting symptoms at diagnosis of DM. Compared with women with normal

### Table 1. Baseline (1989) Characteristics of Study Participants as a Function of Unusual Menstrual Cycle Pattern at Age 18 to 22 Years*

<table>
<thead>
<tr>
<th>Usual Cycle Length, d</th>
<th>No.</th>
<th>Age, y</th>
<th>Body mass index, kg/m²</th>
<th>Age 18 y</th>
<th>In 1989</th>
<th>Weight gain from age 18 y, kg</th>
<th>Physical activity in 1989, METs per wk†</th>
<th>White, %</th>
<th>Family history of DM in first-degree relative, %</th>
<th>Current smoker, %</th>
<th>Irregular cycles, age 18-22 y, %</th>
<th>Severe acne during teenage years, %</th>
<th>Physician-diagnosed hirsutism, %</th>
<th>Ovulatory infertility, %</th>
<th>Ever used oral contraceptives, %‡</th>
<th>Parity</th>
<th>History of gestational DM, %§</th>
<th>Person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21</td>
<td>7</td>
<td>21.3 (4.1)</td>
<td>21.3 (3.4)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.5 (3.9)</td>
<td>31.3 (47.6)</td>
<td>28.6 (42.7)</td>
<td>24.6 (36.1)</td>
<td>22.6 (32.9)</td>
<td>25.5 (39.5)</td>
<td>85</td>
<td>18.1</td>
<td>15.3</td>
<td>12.8</td>
<td>9.9</td>
<td>11.8</td>
<td>1.12 (0.70-3.21)</td>
</tr>
<tr>
<td>21-25</td>
<td>51</td>
<td>21.3 (3.4)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.5 (3.9)</td>
<td>31.3 (47.6)</td>
<td>28.6 (42.7)</td>
<td>24.6 (36.1)</td>
<td>22.6 (32.9)</td>
<td>25.5 (39.5)</td>
<td>88</td>
<td>22.2</td>
<td>15.2</td>
<td>9.7</td>
<td>52.2</td>
<td>95.4</td>
<td>1.18 (0.87-1.60)</td>
</tr>
<tr>
<td>26-31†</td>
<td>257</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.5 (3.9)</td>
<td>31.3 (47.6)</td>
<td>28.6 (42.7)</td>
<td>24.6 (36.1)</td>
<td>22.6 (32.9)</td>
<td>25.5 (39.5)</td>
<td>92</td>
<td>22.2</td>
<td>15.2</td>
<td>9.7</td>
<td>52.2</td>
<td>95.4</td>
<td>1.18 (0.87-1.60)</td>
</tr>
<tr>
<td>32-39</td>
<td>71</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.5 (3.9)</td>
<td>31.3 (47.6)</td>
<td>28.6 (42.7)</td>
<td>24.6 (36.1)</td>
<td>22.6 (32.9)</td>
<td>25.5 (39.5)</td>
<td>93</td>
<td>22.2</td>
<td>15.2</td>
<td>9.7</td>
<td>52.2</td>
<td>95.4</td>
<td>1.18 (0.87-1.60)</td>
</tr>
<tr>
<td>≥40 or Highly Irregular</td>
<td>7734</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.2 (3.3)</td>
<td>21.5 (3.9)</td>
<td>31.3 (47.6)</td>
<td>28.6 (42.7)</td>
<td>24.6 (36.1)</td>
<td>22.6 (32.9)</td>
<td>25.5 (39.5)</td>
<td>92</td>
<td>18.1</td>
<td>15.3</td>
<td>12.8</td>
<td>9.9</td>
<td>11.8</td>
<td>1.00 (0.70-1.40)</td>
</tr>
</tbody>
</table>

*Values are expressed as age-adjusted means and SDs unless otherwise indicated. DM indicates diabetes mellitus.†Average metabolic equivalents (METs) per week calculated by frequency and duration of participation in several aerobic activities. See “Methods” for further details.‡History of oral contraceptive use of 2 months or more.§Reported gestational DM among women reporting at least 1 pregnancy lasting 6 months or more.

### Table 2. Relative Risks (RRs) for Type 2 Diabetes Mellitus Associated With Menstrual Cycle Pattern at Age 18 to 22 Years

<table>
<thead>
<tr>
<th>Usual Cycle Length, d</th>
<th>&lt;21</th>
<th>21-25</th>
<th>26-31†</th>
<th>32-39</th>
<th>≥40 or Highly Irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>5633</td>
<td>56412</td>
<td>372971</td>
<td>86243</td>
<td>43074</td>
</tr>
<tr>
<td>Age-adjusted RR (95% confidence interval)</td>
<td>1.55 (0.73-3.29)</td>
<td>1.18 (0.88-1.59)</td>
<td>1.04 (0.80-1.35)</td>
<td>2.40 (1.88-3.07)</td>
<td></td>
</tr>
<tr>
<td>Multivariate RR (95% confidence interval)</td>
<td>1.50 (0.70-3.19)</td>
<td>1.18 (0.87-1.58)</td>
<td>1.03 (0.79-1.33)</td>
<td>2.08 (1.62-2.66)</td>
<td></td>
</tr>
</tbody>
</table>

*Person-years reflects follow-up time from return of baseline (1989) questionnaire.†Referent.‡Adjusting for age (continuous), time period (3 categories), body mass index at age 18 years (6 categories), smoking (current, past, never), family history of diabetes mellitus in a first-degree relative, physical activity level (quintiles of total metabolic expenditure), and duration of oral contraceptive use.
Menstrual cycle length (26-31 days), RRs for symptomatic DM associated with long cycles remained statistically significant and comparable to those in the primary analyses: RR, 1.82 (95% CI, 1.35-2.44) in multivariate analyses adjusting for BMI at age 18 years, physical activity level, smoking, family history of DM in a first-degree relative, and oral contraceptive use. Short cycles (<21 days) were not associated with a significant increase in DM risk (multivariate RR, 1.36; 95% CI, 0.56-3.33). In addition, 89.4% of the cohort reported a routine physician visit in the previous 2 years, and results were materially unchanged in analyses limited to these women.

A history of oral contraceptive use of at least 2 months' duration was highly prevalent at baseline (1989) regardless of cycle length (Table 1). To minimize the possibility that oral contraceptive use in women with oligomenorrhea might modify risk for DM, we conducted an analysis excluding women reporting any history of oral contraceptive use of 2 months or more prior to study entry in 1989. Among this small subgroup (n=107 cases), long or highly irregular menstrual cycles remained a significant predictor of type 2 DM (data not shown); the small number of cases with a cycle length of less than 21 days precluded valid assessment of the RR associated with short cycles. We also conducted an analysis updating for oral contraceptive use through the study period, and results remained essentially unchanged.

The association between long or highly irregular cycles and subsequent diagnosis of type 2 DM was materially unchanged in additional analyses adjusting for race or for a history of hypertension and antihypertensive therapy. Furthermore, results were comparable in an analysis excluding women who reported a history of infertility treatment (data not shown).

When menstrual cycle patterns at age 18 to 22 years were assessed by the question on cycle regularity, associations between menstrual cycle abnormalities and type 2 DM persisted. Compared with women reporting cycles that were usually or always regular, women reporting cycles that were usually or always irregular or no cycles had a multivariate RR for type 2 DM of 1.52 (95% CI, 1.26-1.83).

**COMMENT**

Among this large cohort of women, oligomenorrhea at the age of 18 to 22 years was a significant predictor of subsequent development of type 2 DM. This observation was not explained simply by associated obesity or several other potential confounding variables. In a cross-sectional study, Roumain et al reported an increased likelihood of type 2 DM among Pima Indian women with a menstrual cycle length of 3 months or more, although the risk increase was not statistically significant after adjustment for obesity. In analyses stratified by BMI, the association between oligomenorrhea and DM was most pronounced among the least obese women, ie, BMI less than 30 kg/m², whereas rates of DM were high among more obese women regardless of cycle characteristics.

Among our population, the average BMI was much lower than among the Pima women, as were the rates of type 2 DM. Using a less extreme definition of oligomenorrhea, we found significant associations between oligomenorrhea and type 2 DM among women with high BMI (≥30 kg/m²) as well as lower BMI at age 18 years.

A high rate of glucose intolerance is well-recognized among women with PCOS, a condition typically defined by the presence of both oligomenorrhea and androgen excess. Studies involving oral glucose tolerance testing among women with PCOS demonstrated impaired glucose tolerance in 31% to 35% and DM in 7.5% to 10%. Abnormalities of glucose homeostasis are greatest in obese women with PCOS but are also seen in nonobese women with this condition. Insulin resistance is characteristic of PCOS and appears to underlie these observations. Women with PCOS have

### Table 3. Multivariate Relative Risks for Type 2 Diabetes Mellitus (DM) Associated With Menstrual Cycle Pattern at Age 18 to 22 Years in Different Subgroups of Women

<table>
<thead>
<tr>
<th>Usual Cycle Length, d</th>
<th>&lt;21</th>
<th>21-25</th>
<th>26-31†</th>
<th>32-39</th>
<th>≥40 or Highly Irregular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hirsutism and/or severe acne during teenage years</strong> Yes (n = 93)</td>
<td>3.85 (1.34-11.11)</td>
<td>1.26 (0.61-2.58)</td>
<td>1.0</td>
<td>0.69 (0.35-1.37)</td>
<td>1.46 (0.86-2.49)</td>
</tr>
<tr>
<td>No (n = 414)</td>
<td>0.80 (0.26-2.51)</td>
<td>1.16 (0.84-1.62)</td>
<td>1.0</td>
<td>1.08 (0.82-1.44)</td>
<td>2.11 (1.59-2.80)</td>
</tr>
<tr>
<td><strong>Body mass index at age 18 y, kg/m²‡</strong> &lt;25 (n = 268)</td>
<td>1.59 (0.59-4.31)</td>
<td>1.37 (0.94-1.99)</td>
<td>1.0</td>
<td>0.79 (0.54-1.16)</td>
<td>1.67 (1.14-2.45)</td>
</tr>
<tr>
<td>25-29.9 (n = 138)</td>
<td>1.03 (0.14-7.52)</td>
<td>0.81 (0.42-1.56)</td>
<td>1.0</td>
<td>1.19 (0.74-1.90)</td>
<td>1.74 (1.07-2.82)</td>
</tr>
<tr>
<td>≥30 (n = 89)</td>
<td>2.22 (0.92-9.41)</td>
<td>1.48 (0.68-3.21)</td>
<td>1.0</td>
<td>1.69 (0.92-3.12)</td>
<td>3.86 (2.33-6.38)</td>
</tr>
<tr>
<td><strong>Family history of DM in first-degree relative</strong> Yes (n = 206)</td>
<td>3.18 (1.38-7.34)</td>
<td>1.63 (1.08-2.48)</td>
<td>1.0</td>
<td>0.98 (0.64-1.50)</td>
<td>1.86 (1.22-2.84)</td>
</tr>
<tr>
<td>No (n = 301)</td>
<td>0.35 (0.05-2.53)</td>
<td>0.86 (0.55-1.35)</td>
<td>1.0</td>
<td>1.06 (0.75-1.46)</td>
<td>2.16 (1.59-2.85)</td>
</tr>
</tbody>
</table>

*Results are expressed as multivariate relative risks (95% confidence intervals); ‡n reflects the total number of cases among women in a given stratum. Adjustment was made for age (continuous), time period (3 categories), body mass index at age 18 years (6 categories), smoking (current, past, never), family history of DM in a first-degree relative, physical activity level (quintiles of total metabolic expenditure), and duration of oral contraceptive use, but not for the stratifying variable.

†Referent.

‡Total n = 495 for stratified analysis due to missing body mass index data.
higher fasting and postprandial insulin levels, and their acute insulin responses to a glucose load are inappropriately low for the magnitude of peripheral insulin resistance. Insulin resistance and associated β-cell dysfunction appear to predispose to type 2 DM, and high insulin levels have predicted progression to type 2 DM among high-risk populations. Concomitant hyperandrogenism, when present, may have a direct adverse effect on insulin resistance and is also associated with reduced levels of sex hormone-binding globulin, a marker for reduced insulin sensitivity that predicts risk for type 2 DM in women.

While PCOS is classically defined by both anovulation and hyperandrogenism, oligomenorrhea in the absence of obvious androgen excess may also frequently be attributable to PCOS. Studies have reported elevated luteinizing hormone levels in 90% of oligomenorrheic women and polycystic ovaries on ultrasonography in 87%. Elevated testosterone levels have likewise been reported in women with oligomenorrhea in the absence of clinical hyperandrogenism. Greater insulin resistance and higher androgen levels have been noted among Pima Indian women with long menstrual cycles.

Menstrual irregularities other than long cycles may also be consistent with PCOS. We found that risk for type 2 DM was significantly higher in women who reported “irregular cycles” irrespective of cycle length. Risk of DM also appeared higher in women who reported a cycle length of less than 21 days, although there were relatively few women in this category and findings were not statistically significant.

While long or irregular cycles are likely to be a marker of PCOS, other possible causes of oligomenorrhea must be considered. Estrogen deficiency consistent with hypogonadotropic hypogonadism is observed in a minority of women presenting with oligomenorrhea or amenorrhea. This condition is commonly associated with weight loss, excessive exercise, or low body weight, factors that would be expected to have a protective effect on development of DM. Inclusion in the current study of oligomenorrheic women with this condition, or with other conditions unassociated with DM, would lead to underestimation of the risk associated with PCOS.

Importantly, absolute rates of DM in this cohort were relatively low overall, reflecting the relatively young age of the women who, after 8 years of follow-up, ranged from 32 to 51 years old. The presence of obesity in addition to oligomenorrhea conferred much greater absolute risk for DM than did oligomenorrhea alone, consistent with previous observations that obesity is a major modifiable risk factor for DM. Previous studies in women with documented PCOS have indicated that weight loss reduces insulin resistance and hyperandrogenism and that leaner women have lower rates of DM.

We found that oligomenorrhea was associated with subsequent type 2 DM even among women who did not report severe teenage acne or hirsutism. However, we were not able to assess comprehensively the prevalence of clinical androgen excess and did not have biochemical measures of hyperandrogenism.

One third or more of DM cases are undiagnosed in the general population. While screening bias, i.e., greater screening for DM in the women with irregular cycles, might contribute to the observed results, we consider this an unlikely explanation. It is possible that women with cycle irregularity may have seen a physician more frequently, but most women in this cohort of health professionals received routine health care, and the association between oligomenorrhea and DM was unchanged in analyses limited to those who had recently seen a physician. Also, until this year, PCOS was not among the conditions for which the American Diabetes Association recommended DM screening, and such screening is not recommended on the basis of menstrual irregularity alone. Furthermore, results of analyses limited to women presenting with symptomatic DM, in whom screening bias would be unlikely to explain results, yielded comparable results. Diagnostic criteria for DM changed after the time women in this cohort were diagnosed, so that some women classified as non-diabetic would now be considered cases; however, this would not affect the validity of the findings.

Because oral contraceptives may adversely affect insulin sensitivity and glucose tolerance, a potential concern is that greater oral contraceptive use among women with irregular cycles might underlie increased DM risk among these women. However, neither adjustment for duration of oral contraceptive use, nor exclusion of women reporting a history of oral contraceptive use, materially changed the results. In addition, a previous NHS analysis did not find an appreciable increase in DM risk with prior use of oral contraceptives.

A limitation of this study is that cycle characteristics are self-reported retrospectively. Nevertheless, the observed frequency of long or highly irregular cycles was comparable to that among college students studied cross-sectionally. Women whose long or irregular menstrual cycles were normalized by treatment with oral contraceptives might have classified their cycles as normal; however, such misclassification would tend to bias toward the null. Duration of menstrual periods was not assessed.

This study indicates that long or highly irregular menstrual cycles are a predictor of increased risk for type 2 DM, and that this risk is further increased by, but not completely explained by, obesity. These findings are consistent with the suggestion of previous cross-sectional studies that menstrual cycle irregularities may be a marker for associated metabolic abnormalities and suggest that women with this history might particularly benefit from lifestyle approaches to reduce risk, such as weight control and exercise.


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REFERENCES


Don’t be “consistent” but be simply true.
—Oliver Wendell Holmes (1809-1894)