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Menstrual Cycle Irregularity and Risk for Future Cardiovascular Disease

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Cross-sectional studies suggest that women who have irregular menstrual cycles and hyperandrogenism may be at increased risk for cardiovascular disease (CVD). However, prospective data are lacking on the relationship between menstrual cycle irregularity and subsequent CVD risk. The objective of this study was to assess prospectively the risk for coronary heart disease (CHD) and stroke associated with a history of irregular menstrual cycles. The study design was a prospective cohort study of 82,439 female nurses who provided information in 1982 on prior menstrual regularity (at ages 20–35 yr) and were followed through 1996 for cardiovascular events. Incident reports of nonfatal myocardial infarction, fatal CHD, and nonfatal and fatal stroke were made. Medical records were reviewed for confirmation.

During 14 yr (1,155,915 person-yr) of follow-up, there were 1417 incident cases of CHD and 838 incident cases of stroke, including 471 cases of ischemic stroke. Compared with women reporting a history of very regular menstrual cycles, women reporting usually irregular or very irregular cycles had an increased risk for nonfatal or fatal CHD [age-adjusted relative risks (RR), 1.25 and 1.67, respectively; 95% confidence intervals (CI), 1.07–1.47 and 1.35–2.06, respectively]. Increased risks for CHD associated with prior cycle irregularity remained significant after adjustment for body mass index and several potential confounders. There was a nonsignificant increase in overall stroke risk (RR, 1.30; 95% CI = 0.97–1.74) and in ischemic stroke risk (RR, 1.40; 95% CI = 0.97–2.04) associated with very irregular cycles.

Menstrual cycle irregularity may be a marker of metabolic abnormalities predisposing to increased risk for CVD. (*J Clin Endocrinol Metab* 87: 2013–2017, 2002)

MENSTRUAL IRREGULARITY may be a marker for underlying insulin resistance (1–3). In population-based studies, oligomenorrhea has been associated with hyperinsulinemia (1) and with increased prevalence (4) and future risk of type 2 diabetes mellitus (5). These findings are likely to reflect the fact that polycystic ovary syndrome, a syndrome characterized by anovulation, androgen excess, and insulin resistance (2), is a frequent cause of oligomenorrhea (6).

Insulin resistance is associated with type 2 diabetes mellitus, hypertension, and dyslipidemia (7); through these and other mechanisms, this condition may predispose to cardiovascular disease (CVD). Women with polycystic ovary syndrome (PCOS) have increased rates of diabetes (8) and dyslipidemia (9) and higher blood pressure (9) compared with normally cycling women. Correspondingly, it has been suggested that the risk for coronary heart disease (CHD) is increased in women with this condition (10). However, limited prospective data in women with PCOS have failed to show increased rates of coronary disease (11) or cardiovascular mortality (12).

Prospective data are lacking on the relationship between irregular menstrual cycles and subsequent CVD. To assess whether menstrual cycle irregularity is a marker for later risk of CHD and stroke in women, we studied participants in the Nurses' Health Study, a large prospective study of female registered nurses.

Abbreviations: CHD, Coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; PCOS, polycystic ovary syndrome; RR, relative risk.

Materials and Methods

The Nurses' Health Study is a prospective cohort study of 121,700 female nurses, aged 30–55 yr at study inception in 1976, residing in 1 of 11 U.S. states. The cohort is 98% Caucasian. Participants complete biennial questionnaires on lifestyle factors and medical conditions. This study is approved by the institutional review board of Brigham and Women's Hospital. Participants are informed that return of the questionnaires is voluntary, and return of the questionnaire is considered to indicate consent to participate.

The present investigation included 82,439 women who responded to a 1982 question asking about prior usual menstrual cycle regularity at ages 20–35 yr and who did not have a history of CHD (including myocardial infarction, angina, and/or coronary revascularization), stroke, or cancer (other than nonmelanoma skin cancer). Women reporting these morbidities on or before the 1982 questionnaire were excluded at baseline, and women reporting CHD or stroke on subsequent questionnaires were excluded from further analysis.

Menstrual cycle regularity

The usual menstrual cycle pattern was assessed in 1982 by the question: which best describes the regularity of your usual menstrual periods between ages 20 and 35 when you were neither pregnant nor using oral contraceptives? Response choices and distribution of follow-up time were as follows: very regular (715,293 person-yr, 61.9%), usually regular (264,924 person-yr, 22.9%), usually irregular (126,406 person-yr, 10.9%), and very irregular (49,292 person-yr, 4.3%).

In an effort to validate self-reported menstrual irregularity, we used data from the Nurses' Health Study II, a companion cohort of younger

nurses who were asked to report on current cycle regularity and usual cycle length in 1993, when their age range was 29–48 yr. We limited our comparison group to women 29–35 yr of age at the time the question was asked (n = 26,421) to overlap with the age range for which cycle patterns were retrospectively reported in the present study. The concordance was extremely high, with 87% of the women reporting cycles that were regular (in comparison with 85% in the present cohort) and 12% reporting usually or always irregular cycles or no menses (compared with 15% in the present cohort). Among women in this comparison group reporting regular cycles, 75% reported usual cycle length of 26–31 d, and only 1.5% reported usual cycle length less than 21 d or 40 d or more. In contrast, of those reporting cycles that were always irregular, only 7.4% reported usual cycle length of 26–31 d, whereas 70.3% reported cycles that were very short (<21 d) or long (40 d or more).

Prior validation studies in the cohort have confirmed a high accuracy of self-report for such variables as body weight (13), diabetes mellitus (14), and hypertension and hypercholesterolemia (15).

Cardiovascular end points

Biennial questionnaires also asked whether participants had had a diagnosis of myocardial infarction in the preceding 2-yr interval, and those who reported myocardial infarction were asked for permission to review their medical records. Self-reports of nonfatal myocardial infarction were considered confirmed if information in the medical record met the following WHO criteria: characteristic symptoms with either diagnostic electrocardiographic changes and/or cardiac enzyme elevation. We excluded silent myocardial infarctions that were noted on a routine electrocardiogram, as information was not systematically collected for these cases. If there were no available hospital records for self-reported myocardial infarction, but hospitalization was confirmed and information from an interview or letter supported the diagnosis, self-reported diagnosis was considered probable. Probable cases, which comprised 17% of the total cases, were included in analyses.

Strokes were also confirmed by medical record review, using criteria established by the National Survey of Stroke (16): evidence of a typical neurological deficit of sudden or rapid onset, persisting for more than 24 h or until death. Strokes due to traumatic, neoplastic, or infectious processes were excluded, as were clinically silent strokes noted only by radiological imaging. If hospital records could not be obtained but a participant reported a stroke that required hospitalization, and additional information was available from letter or phone interview, an incident stroke was considered probable. In previous reports results including probable stroke cases (25% of total) were comparable to results using only confirmed cases (17); both confirmed and probable cases were included in the present analyses. Strokes were also subclassified as ischemic (due to thrombotic or embolic occlusion of a cerebral artery), hemorrhagic (due to either subarachnoid or intraparenchymal hemorrhage), and unknown (documented stroke for which the subtype could not be determined). We performed a secondary analysis limited to strokes considered to be ischemic, and for this analysis excluded hemorrhagic strokes and those for which the etiology was unclear.

Total CVD events were considered to be the combination of nonfatal myocardial infarction, fatal CHD, and nonfatal and fatal stroke. Deaths were generally reported by family members of participants. We also used the National Death Index to search for deaths among women who did not respond to a questionnaire. The follow-up rate was 98%. For mortality considered due to CVD, permission to review records was requested from the next of kin. A fatal myocardial infarction was confirmed if medical records or autopsy report indicated this diagnosis, or if the death certificate reported coronary disease as the cause of death, the participant was known to have coronary disease previously (by questionnaire or per next of kin), and there was no other more likely cause apparent. Fatal coronary disease was also diagnosed if there was sudden death, *i.e.* death within 1 h of symptom onset in a woman without known disease that could explain this. Fatal strokes were confirmed by medical records, autopsy findings, or the listing of stroke on the death certificate as the underlying cause of death.

Statistical analysis

Women were divided into categories based on usual menstrual cycle characteristics at ages 20–35 yr, as reported in 1982. Incidence rates were calculated by dividing the number of events by the person-time of follow-up for each category. Relative risks (RR) and 95% confidence intervals (CI) were calculated as the rate for a given category of cycle irregularity compared with the referent category (very regular).

Pooled logistic regression (18) with 2-yr increments was used to model risks for coronary disease and stroke in relation to cycle regularity, adjusting for potential confounders, including age (5-yr intervals), body mass index (5 categories), cigarette smoking (never, past, or current smoking of 1–14, 15–24, or >25 cigarettes/d), menopausal status (premenopausal, postmenopausal without hormone replacement, postmenopausal with past hormone replacement, postmenopausal with current hormone replacement), parental history of myocardial infarction before age 60 yr (yes/no), parity (0, 1–2, 3–4, 5+), alcohol intake (none, 1–4, 5–15, or >15 g/d), aspirin use (<1 time/wk, 1–6 times/wk, >7 times/week), multivitamin use (yes/no), use of vitamin E supplements (yes/no), physical activity level (times per week of vigorous exercise: <1, ≥1 time/wk, 1–3 times/week, >4 times/wk) and history of oral contraceptive use (never, <3, 3–5, >5 yr). Because usual menstrual cycle characteristics were assessed in 1982, most baseline information for these analyses was derived from the 1982 questionnaire. Information on physical activity came from the 1980 questionnaire, as this was not assessed in 1982. Covariates other than physical activity level and oral contraceptive use were updated based on information provided on subsequent questionnaires. Secondary analyses were also adjusted for personal history of diabetes mellitus, hypertension, and hypercholesterolemia.

Results

Table 1 demonstrates baseline (1982) characteristics of the cohort as a function of prior menstrual cycle pattern at age 20–35 yr. Women reporting cycles that were usually irregular or very irregular tended to have higher body mass index and were more likely to report histories of diabetes mellitus, hypertension, and hypercholesterolemia than women with a history of regular menstrual cycles. These abnormalities were particularly common in women with very irregular cycles. However, smoking habits, use of aspirin and vitamin supplements, and physical activity level did not vary appreciably by prior cycle regularity.

During 14 yr (1,155,915 person-yr) of follow-up, there were a total of 2,255 cardiovascular events among this population. These included 1,417 CHD events (964 cases of nonfatal myocardial infarction and 453 cases of fatal CHD) and 838 strokes (471 of which were considered ischemic strokes).

Compared with women reporting a history of very regular menstrual cycles, women reporting usually regular menstrual cycles had similar risks for CHD. In contrast, women reporting usually irregular or, in particular, very irregular cycles were at significantly increased risk for CHD (Table 2). For women with very irregular cycles, compared with those whose cycles were very regular, the age-adjusted RR for CHD was 1.67 (95% CI = 1.35–2.06), and this elevated risk remained statistically significant in analyses also adjusting for body mass index, cigarette smoking, parity, oral contraceptive use history, alcohol intake, aspirin, multivitamin use, vitamin E use, menopausal status, and postmenopausal hormone use (RR = 1.53; 95% CI = 1.24–1.90; trend for increasing irregularity, $P < 0.0001$). Increased risks were observed for both nonfatal myocardial infarction (multivariate RR = 1.38; 95% CI = 1.06–1.80) and fatal CHD (multivariate RR = 1.88; 95% CI = 1.32–2.67).

Stratified analyses were performed to assess the impact of other factors on the association between irregular cycles and CHD risk. In analyses limited to women with complete up-

TABLE 1. Baseline (1982) characteristics of women as a function of prior menstrual cycle regularity at ages 20–35 yr

	Cycle regularity			
	Very regular	Usually regular	Usually irregular	Very irregular
Age (yr)	47.8	48.6	48.2	48.3
Body mass index (kg/m^2)	24.6	24.5	24.7	25.4
Current smoker (%)	26	26	27	29
Parental MI (%)	20	20	21	22
Hypertension (%)	17	19	20	23
Diabetes mellitus (%)	1.8	2.1	2.7	4.3
High cholesterol (%)	5.8	6.2	6.7	8.9
Current postmenopausal hormone use (%)	16	17	16	18
Multivitamin use (%)	32	32	32	31
Vitamin E supplement use (%)	12	12	12	12
Regular physical activity (%)	43	42	42	41
Daily alcohol (g)	6.6	6.1	6.1	5.9

All variables, except age, are age-adjusted. Values are means or percentages. Parental MI, Parental history of myocardial infarction less than 60 yr of age. Regular physical activity refers to those who reported engaging in physical activity vigorous enough to perspire at least once per week. Regular ASA use refers to those who reported taking on average one aspirin or more per week.

TABLE 2. RRs for CHD as a function of menstrual cycle regularity at ages 20–35 yr

	Menstrual cycle regularity ages 20–35 yr				*P* trend
	Regular	Usually regular	Usually irregular	Very irregular	
Total CHD					
No. of cases	810	327	184	96	
Person-yr	715,293	264,924	126,406	49,292	
Age-adjusted RR (95% CI)	1.0	1.02 (0.90–1.16)	1.25 (1.07–1.47)	1.67 (1.35–2.06)	<0.001
Multivariate[a] RR (95% CI)	1.0	1.02 (0.89–1.16)	1.22 (1.04–1.44)	1.53 (1.24–1.90)	<0.001
Nonfatal CHD					
No. of cases	562	210	132	60	
Age-adjusted RR (95% CI)	1.0	0.95 (0.81–1.11)	1.30 (1.07–1.60)	1.50 (1.15–1.96)	0.001
Multivariate[a] RR (95% CI)	1.0	0.96 (0.82–1.12)	1.27 (1.05–1.54)	1.38 (1.06–1.80)	0.005
Fatal CHD					
No. of cases	248	117	52	36	
Age-adjusted RR (95% CI)	1.0	1.17 (0.94–1.46)	1.16 (0.86–1.56)	2.04 (1.44–2.89)	0.001
Multivariate[a] RR (95% CI)	1.0	1.12 (0.90–1.40)	1.11 (0.82–1.50)	1.88 (1.32–2.67)	0.005

[a] Adjusting for age, body mass index, cigarette smoking, menopausal status/postmenopausal hormone use, parential history of MI before age 60 yr, parity, alcohol intake, aspirin use, multivitamin use, vitamin E supplement use, physical activity level, and history of oral contraceptive use.

dated information on body mass index, the association between cycle irregularity and CHD appeared stronger among overweight than lean women. Among women with a body mass index of 25 kg/m^2 or more (n = 691 cases), the multivariate RR for usually irregular cycles was 1.57 (95% CI = 1.27–1.96), and that for very irregular cycles was 1.50 (95% CI = 1.10–2.04), whereas among women whose body mass index was less than 25 kg/m^2 (n = 496 cases), multivariate RRs for usually irregular and very irregular cycles were 0.99 (CI = 0.75–1.32) and 1.28 (CI = 0.86–1.89), respectively.

We found no material differences in observed associations between cycle irregularity and CHD as a function of cigarette smoking, parental history of myocardial infarction, and use of postmenopausal hormone replacement therapy (Data not shown). Relative risks for CHD associated with irregular cycles were comparable among those who were never users of oral contraceptives (multivariate RR for very irregular cycles 1.64; 95% CI = 1.25–2.15) and those who had a history of oral contraceptive use (multivariate RR = 1.37; 95% CI = 0.97–1.94). Results were also similar when we excluded women reporting menopause before age 40 yr, in whom cycle irregularity may be more likely to reflect declining ovarian function; the multivariate relative risk for CHD associated with usually irregular cycles was 1.28 (95% CI = 1.08–1.52), and, for very irregular cycles, was 1.54 (95% CI = 1.20–1.97).

Because associated insulin resistance was a presumed mechanism through which irregular cycles might be linked to CHD, we purposely did not adjust for diabetes mellitus, hypertension, or hypercholesterolemia in the primary analyses. However, we did perform supplemental analyses adjusting for these variables in addition to potential confounders noted above; we found that the relationship between irregular menstrual cycles and CHD was attenuated, although not eliminated. Compared with women reporting a history of very regular cycles, the multivariate relative risk for CHD among women reporting a history of usually irregular cycles was 1.14 (95% CI = 0.97–1.34), and that for women reporting very irregular cycles was 1.34 (95% CI = 1.08–1.66).

The risk for stroke was slightly, although not significantly, elevated among women with a history of irregular menstrual cycles. The multivariate RR for stroke associated with usually irregular cycles was 1.04 (95% CI = 0.84–1.30); for very irregular cycles, the RR was 1.30 (95% CI = 0.97–1.74). When the analysis was limited to ischemic stroke (n = 471 cases),

the multivariate RR associated with very irregular cycles was 1.40 (95% CI = 0.97–2.04).

We also considered all CVD events combined (nonfatal and fatal CHD and stroke). A history of usually irregular menstrual cycles was associated with a multivariate RR of CVD of 1.17 (95% CI = 1.03–1.33), and a history of very irregular cycles was associated with a multivariate RR of 1.46 (95% CI = 1.23–1.74).

Discussion

We observed a 50% greater risk of nonfatal myocardial infarction or fatal CHD among women with a history of very irregular menstrual cycles at ages 20–35 yr compared with women reporting a history of very regular cycles. Women with a history of cycle irregularity also had a tendency to higher risk of stroke, specifically ischemic stroke, although this association was not statistically significant. Because coronary disease events comprised the majority of cardiovascular events, the risk of overall CVD was also significantly increased among women with a history of very irregular menstrual cycles.

The most likely explanation is that many women with menstrual irregularity have PCOS, which has been linked to metabolic abnormalities that predispose to CVD. Because we do not have information on clinical or biochemical androgen excess among our study cohort, we cannot confirm the diagnosis of PCOS in women with cycle irregularity. We also did not have information on menorrhagia or procedures such as curettage.

However, prior studies suggest that PCOS is frequently the explanation for irregular menstrual cycles. In a study involving 247 women with oligomenorrhea or amenorrhea (6), 90% of those with oligomenorrhea and 73% of those with either menstrual disturbance had laboratory and/or clinical findings consistent with PCOS. In another report (19) 87% of women with oligomenorrhea had polycystic ovaries documented on ultrasonography, the majority of whom also had elevated LH and/or T levels. Increased T levels have been reported even in nonhirsute women with oligomenorrhea (20, 21).

Several coronary risk factors have been well described in women with PCOS, including elevated rates of obesity (9, 10, 22, 23), central obesity (9), glucose intolerance (24–27), and increased blood pressure (9, 24). Increased insulin resistance (2) has been observed even in nonobese women with PCOS. Lipid abnormalities (28), including increased levels of triglyceride (9, 22, 23, 29), low density lipoprotein, and total cholesterol levels (9, 23) and reduced levels of high density lipoprotein (9, 23, 29), have been reported among younger women with PCOS, although were not observed in two studies involving fifth decade and older women with PCOS (22, 27). We observed an increased frequency of diabetes mellitus, hypertension, and hypercholesterolemia among mostly postmenopausal women with a history of menstrual irregularity.

Cross-sectional data have suggested increased rates of CHD among women with PCOS. Increased atherosclerosis at cardiac catheterization has been reported among women with polycystic ovaries (30) or hirsutism (31) suggestive of hyperandrogenism, and premature carotid atherosclerosis has been observed among women with oligomenorrhea and androgen excess (32). In a small study involving perimenopausal women, those with PCOS were more likely to report a history suggestive of CHD (27), although this diagnosis was not validated.

Based on observed coronary risk factors among women with PCOS, Dahlgren and colleagues (10) predicted a 7-fold increased risk for myocardial infarction among affected women, but their study group was too small to evaluate the accuracy of this estimate However, data from a long-term follow-up study of women with PCOS failed to demonstrate significant increases in CHD morbidity (11) or cardiovascular mortality (12) and a lower than expected risk for fatal cerebrovascular disease. Nonetheless, the relative risks for fatal CVD and prevalent CHD associated with PCOS in those studies (1.5 and 1.4, respectively) are highly consistent with the magnitude of fatal and nonfatal CHD risk observed among women with menstrual irregularity in the present report. In contrast to the prior study in women with documented PCOS (12), which was based on a small number of end points, we observed a nonsignificantly higher risk for stroke overall and for ischemic stroke in particular among women with a history of irregular menses.

The association between cycle irregularity and CHD was slightly attenuated, although still significant, after adjustment for body mass index and was less apparent when analyses were limited to lean women. These observations suggest that obesity is an important contributor to the relationship between irregular cycles and CHD risk.

Conditions other than PCOS also may have caused irregular menstrual cycles. Premature menopause is associated with menstrual cycle abnormalities at early ages and is also associated with increased CHD risk (33). However, results were unchanged when we excluded women who reported menopause before age 40 yr. Although estrogen deficiency related to hypogonadotropic hypogonadism might be anticipated to increase coronary risk, this condition is an infrequent cause of irregular cycles (6). Furthermore, insofar as the majority of cases of hypogonadotropic hypogonadism may be attributed to weight loss or low body weight (6), the fact that the association between cycle irregularity and CHD was not statistically significant among women with body mass index less than 25 kg/m^2 suggests that inclusion of women with this condition is unlikely to explain the observed increase in CHD risk with irregular cycles.

Greater use of oral contraceptives by women with irregular cycles also is unlikely to explain this finding, as this association persisted in analyses limited to women who reported never using oral contraceptives. Moreover, previous work in this cohort has failed to find a significant association between past use of oral contraceptives and risk of CHD (34).

Other potential limitations of the present study should be considered. Misclassification is possible. Cycle characteristics at ages 20–35 yr were self-reported much later in life, when women were between ages 36 and 61 yr. Also, because the questionnaire did not include criteria for women to use in assessing their cycle regularity, individual women may have categorized similar cycle features differently. However, the distribution of cycle regularity reported in this cohort is highly consistent with that reported by younger women in a companion cohort, the Nurses' Health Study II, as well as with observations among other populations of women of

similar age (35, 36). As described in *Materials and Methods*, there was a close correlation in the Nurses' Health Study II between self-described irregular cycles and very short or long cycle lengths. Cycles described as very irregular may have more often been a marker for underlying PCOS than less irregular cycles; this might explain the stronger association between very irregular cycles and CHD than between usually irregular cycles and CHD. We included only CHD end points that occurred after the time that cycle characteristics were reported. Thus, any misclassification of cycle features would be random with respect to outcome and would not explain the observed associations between very irregular cycles and CVD.

In conclusion, these data indicate that a history of irregular menses may be a marker for increased risk of later CVD, in particular, coronary disease. These findings may be explained by a high rate of PCOS and its associated metabolic derangements among women with irregular cycles. Screening for coronary risk factors and counseling regarding healthy lifestyle practices may be particularly important for women with this history.

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