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ARTICLE

Pre-pregnancy menstrual cycle regularity and length and the risk of gestational diabetes mellitus: prospective cohort study

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Abstract

Aims/hypothesis Menstrual cycle dysfunction has been associated with many endocrine-related diseases, but evidence linking menstrual cycle dysfunction with gestational diabetes mellitus (GDM) is scant. The current study investigated the association of pre-pregnancy menstrual cycle regularity and length during adolescence, early adulthood and mid-adulthood with the subsequent risk of GDM.

Methods Between 1993 and 2009, we followed 10,906 premenopausal women participating in the Nurses' Health Study II who reported menstrual cycle characteristics during adolescence (age 14–17 years), early adulthood (age 18–22 years) and mid-adulthood (age 29–46 years). Incident GDM was ascertained from a self-reported questionnaire regarding physician diagnosis. Log-binomial models with generalised estimating equations were used to estimate the RRs and 95% CI for the associations between menstrual cycle characteristics and GDM.

Results We documented 578 incident cases of GDM among 14,418 pregnancies over a 16 year follow-up. After adjusting for potential confounders, women reporting always having irregular menstrual cycles during mid-adulthood had a 65% (95% CI 21, 125%) higher risk of GDM than women reporting very regular cycles. GDM risk was also greater among women reporting that their cycles were usually ≥32 days during mid-adulthood, compared with women reporting cycles between 26 and 31 days (RR 1.42 [95% CI 1.15, 1.75]). The risk of GDM was greater for women whose cycles changed from regular early in their reproductive years to irregular or from <32 days to ≥32 days during mid-adulthood, compared with women whose cycles remained <32 days or regular, respectively.

Conclusions/interpretation Women whose cycles were long or irregular during mid-adulthood, but not in adolescence or young adulthood, were at higher risk of GDM.

Keywords Epidemiology · Gestational diabetes mellitus · Menstrual cycle · Pregnancy · Public health

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Research in context

What is already known about this subject?

- Irregular and long menstrual cycles are common endocrine disorders among women of reproductive age and have been associated with many endocrine-related diseases
- However, evidence linking irregular or long menstrual cycles with gestational diabetes mellitus (GDM) is scarce and inconsistent

What is the key question?

- Are pre-pregnancy menstrual cycle regularity and length during adolescence, early adulthood and mid-adulthood associated with subsequent risk of GDM?

What are the new findings?

- Irregular and long menstrual cycles during mid-adulthood were associated with a greater risk of GDM in later life
- These relations were independent of the BMI determined across the reproductive lifespan, as well as other well known risk factors for GDM

How might this impact on clinical practice in the foreseeable future?

- Our results suggest that menstrual cycle characteristics before pregnancy may serve as early markers for subsequent risk of GDM

Abbreviations

AHEI Alternate Healthy Eating Index
GDM Gestational diabetes mellitus
NHS Nurses' Health Study
OC Oral contraceptive

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition during pregnancy, has become one of the most common pregnancy complications worldwide [1]. The global prevalence of GDM varies from 1.8% to 24.9%, depending on population characteristics, screening methods and diagnostic criteria [2]. In the USA, the prevalence of GDM has increased from 0.3% in 1979–1980 to 7.6% in 2007–2014 [3, 4]. Because GDM is associated with considerable risks to both mothers and the developing fetus [5], it is critical to identify groups with increased susceptibility and develop strategies to promote prevention.

The normal ovulatory menstrual cycle is a vital sign of women's overall health [6]. However, irregular or long menstrual cycles, reflecting functional disruption of the neuroendocrine hypothalamic–pituitary–ovarian (HPO) axis, are estimated to affect nearly 20% of reproductive age women [7]. Menstrual cycle dysfunction has been associated with many endocrine-related diseases, including insulin resistance and type 2 diabetes [8–10]. However, evidence linking irregular or long menstrual cycles with GDM is scant and inconsistent [11, 12]. Inference from previous studies is hampered by limited sample size, poorly characterised cycle patterns (e.g., regular vs irregular) and a lack of information on key confounders including BMI, diet quality and lifestyle factors [11, 12]. More importantly, no study has assessed whether the same phenotype across different stages of a woman's reproductive lifespan (e.g., adolescence, early adulthood and mid-adulthood) has a similar association with GDM. To address these important knowledge gaps, we prospectively investigated the association between pre-pregnancy menstrual cycle regularity and length during adolescence (age 14–17 years), early adulthood (age 18–22 years) and mid-adulthood (age 29–46 years) with the risk of GDM among women participating in a large ongoing prospective cohort study.

Methods

Study population The Nurses' Health Study (NHS) II is an ongoing prospective cohort that was established in 1989 by recruiting 116 429 reproductive age female nurses (age 25–42 years) in the USA [13]. The cohort is followed biennially using validated questionnaires since inception to update participants' lifestyle and dietary variables, medical information and incident diseases. The response rate for each follow-up cycle exceeds 90%. The NHS II protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health

(Protocol number: 2009-P-002375), and those of participating registries as required. Returning completed questionnaires indicates informed consent.

We excluded the women who had missing data on birthday or menstrual cycle characteristics, or those who had received a diagnosis of type 2 diabetes, reached menopause, or had died by 1993 (Fig. 1). Additionally, NHS II participants were eligible for inclusion in the current study if they reported at least one pregnancy lasting >6 months after returning the 1993 questionnaire when cycle characteristics during mid-adulthood were collected. The end of the follow-up was up to the return of the 2009 questionnaire when most participants had passed reproductive age. Finally, 10 906 premenopausal women with 14 418 pregnancies (7832 women had one, 2553 had two, and 521 had three or more pregnancies) were included for our current analysis. Participants' age-adjusted characteristics in 1993 were similar between included women and those excluded because of incomplete data on menstrual cycle characteristics (electronic supplementary material [ESM] Table 1).

Menstrual cycle characteristics In the 1989 questionnaire, participants reported the usual regularity (age 14–17 and 18–22 years) and length (age 18–22 years) of their menstrual cycles, excluding periods of pregnancy or when using oral contraceptives (OC) [14]. Similarly, in 1993 participants reported their current menstrual cycle regularity and length (then age 29–46 years) [14]. Cycle length was reported as '≤21 days', '21–25 days', '26–31 days', '32–39 days', '40–50 days' or '>50 days or too irregular to estimate'. For cycle regularity, questionnaire choices included 'very regular (±3 days)', 'regular', 'usually irregular', 'always irregular' and 'no periods'. Given that OC use affects cycle characteristics, and that OC is often used to treat ovulation disorders [15], we considered women who used OC for more than 2 months per year as a separate exposure group. The reliability of self-reported menstrual cycle questions has been validated previously in other studies and a subgroup of NHS II participants ($n = 26{,}421$) [7, 16]. Among women who reported regular cycles, the majority of women (84.3%) also reported a normal cycle length of 26–31 days; only 0.6% reported extreme cycle length (< 21 days, ≥40 days, or too irregular to estimate) [8]. Likewise, among women who always had irregular cycles, 62.2% reported an extreme cycle length and only 10.3% reported a normal cycle length [8].

GDM ascertainment Women reported incident GDM diagnosis through the biennial questionnaires up to 2003. GDM diagnosed between 2004 and 2009 was ascertained through a 2009 pregnancy questionnaire, which collected retrospective information on all previous pregnancies, including the order and years of births and pregnancy complications. During the period of our current analysis, the National Diabetes Data Group criteria were widely used by physicians for GDM diagnosis. In a validation study conducted among 114 participants from this cohort, 94% of the self-reported GDM events were confirmed by medical records [17]. In another random subgroup of parous women in this cohort who were free of GDM ($n = 100$), 100% of responders underwent frequent prenatal urine screenings during pregnancy and 83% underwent a glucose screening test [17], indicating a high degree of GDM surveillance.

Covariates Participants reported date of birth, height, body weight at age 18, and ethnicity at recruitment. Current body weight, smoking status, OC use, menopausal status, gravidity, infertility history and family history of diabetes were obtained at baseline and then updated biennially. We calculated BMI (kg/m^2) at age 18 and during each follow-up cycle. Physical activity was ascertained in 1997, 2001 and 2005 [18]; we calculated the total hours per week spent on moderate-to-vigorous activities before pregnancy (e.g., brisk walking,

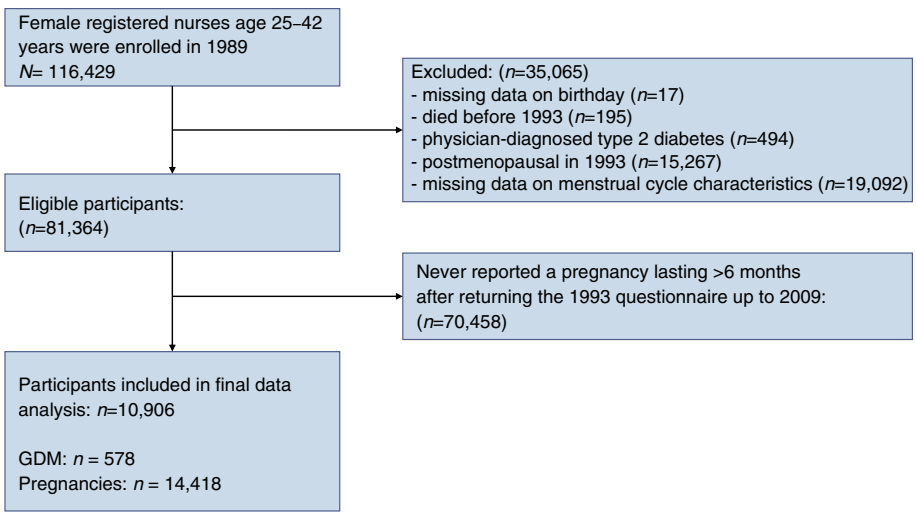

Fig. 1 Flow chart for study population

bicycling, swimming, racquetball, jogging, running and tennis). Dietary intake and alcohol consumption was ascertained every 4 years using a semi-quantitative food frequency questionnaire [19]. The overall dietary quality before pregnancy was assessed by calculating a summary diet score based on the Alternate Healthy Eating Index (AHEI) [20]. The reliability of self-reported body weight, smoking habit, physical activity and diet in this cohort has been validated in previous studies [18, 21, 22].

Patient and public involvement statement This research was done without patient involvement. Patients and the public were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients and the public were not invited to contribute to the writing or editing of this document for readability or accuracy.

Data analysis Participants' characteristics at baseline in 1993 were presented according to the categories of menstrual cycle regularity and length determined during mid-adulthood. To account for potential correlations between repeated pregnancies within individuals, multivariable log-binomial models with generalised estimating equations (GEEs) were applied to estimate the RRs and 95% CIs for the associations of cycle regularity and length during adolescence, early adulthood and mid-adulthood with the risk of incident GDM during follow-up. To assess the effect of change in menstrual cycle patterns across the reproductive lifespan, we cross-classified participants according to their menstrual cycle patterns during adolescence or early adulthood and mid-adulthood. Multivariable models were adjusted for current age (continuous), age at menarche (continuous), BMI at age 18 years (continuous), ethnicity (White or others), family history of diabetes (yes or no) and parity (1, 2, 3 or ≥4). In a secondary multivariable model, we further adjusted for time-varying alcohol consumption (0, 0.1–5.0 or ≥5.1 g/day), BMI (<23, 23–24.9, 25–29.9, 30–34.9 or ≥35 kg/m^2), physical activity (<150 or ≥150 min/week), smoking status (never, past or current) and AHEI 2010 score (below or above median) during follow-up. Information from the previous biennial cycle was carried forward for missing data (<5% for any covariates); otherwise, a separate missing data category was created.

We evaluated effect modification by performing analyses stratified by BMI at age 18 years and in 1993 (<25 vs ≥25 kg/m^2). We also evaluated effect modification by time-varying lifestyle factors (i.e., diet quality, BMI, smoking, physical activity), maternal age, parity and infertility history. Multiplicative interaction was assessed by comparing the multivariable log-binomial models with and without the product term between cycle regularity or length and effect modifiers using the likelihood ratio test [23].

Several sensitivity analyses were conducted to assess the robustness of associations between menstrual cycle characteristics and the risk of GDM. First, we included women in multivariable log-binomial models who provided partial data on menstrual cycle characteristics during adolescence, early adulthood and mid-adulthood to assess the influence of missing data. Second, we reanalysed the associations between menstrual cycle characteristics during adolescence and early adulthood and GDM by including pregnancies reported after the return of the 1989 questionnaire up to the end of 2009 to assess potential selection bias. Third, we excluded women who reported a GDM diagnosis before 1993, as they might have modified their diet and lifestyle in a way that could influence subsequent GDM risk. Fourth, we excluded women older than 40 years in 1993 to reduce the possibility of misclassifying women who experienced early signs of menopause. Fifth, we excluded women reporting 'no period' or '>50 days or too irregular to estimate' from the exposure categories to minimise exposure misclassification. Sixth, we excluded women reporting hirsutism, endometriosis or uterine fibroids to test if our findings were driven by polycystic ovary syndrome or other gynaecological conditions [24]. Seventh, we excluded pregnancies with multiple births (twins or higher). Finally, we restricted our analysis to non-Hispanic White women to explore the potential influence of ethnic or racial minority groups. All analyses were performed with SAS 9.3 for UNIX (SAS Institute, Cary, NC, USA). All tests were two-sided and the p value threshold for a statistical significance was 0.05.

Results

Participants' age-adjusted characteristics according to menstrual cycle regularity and length in 1993 are presented in Table 1. The maternal mean age at pregnancy was 30.80 ± 5.15 years. Among women who did not use OC (8355), 384 (4.6%) reported that their current menstrual cycles were always irregular or they had no periods; 1851 (22.2%) reported that their current cycle length was ≥32 days or too irregular to estimate (Table 1). Compared with women reporting very regular cycles, women who reported they always experienced irregular menstrual cycles or no periods had apparently higher baseline BMI (26.2 ± 6.9 vs 23.5 ± 4.3 kg/m^2) and greater prevalence of family history of diabetes (26.8 vs 19.3%). Similar results were observed among women who reported that their usual cycle length was ≥32 days or too irregular to estimate compared with women reporting a normal cycle length (26–31 days).

We documented 578 incident cases of GDM among 14,418 pregnancies during 16 years of follow-up. Menstrual cycle characteristics during adolescence and early adulthood were not associated with GDM. However, women reporting that

Table 1 Age-standardised baseline characteristics of the study population according to menstrual cycle regularity in mid-adulthood (age 29–46 years) among 10,906 premenopausal women who contributed 14,418 pregnancies from NHS II

Characteristic	Menstrual cycle regularity[a]				Menstrual cycle length[a]		
	Very regular (*n*=5400)	Regular (*n*=2061)	Usually irregular (*n*=510)	Always irregular or no periods (*n*=384)	<26 days (*n*=738)	26–31 days (*n*=5766)	≥32 days or too irregular to estimate (*n*=1851)
Age at menarche, years	12.5 (1.4)	12.7 (1.5)	12.8 (1.7)	12.9 (1.8)	12.4 (1.4)	12.5 (1.4)	12.8 (1.6)
BMI at age 18 years, kg/m^2	21 (2.9)	20.9 (2.9)	21.3 (3.5)	21.5 (3.6)	21.1 (3.3)	20.9 (2.9)	21.1 (3.1)
Current age, years[b]	33.9 (3.1)	33.6 (3.1)	33.1 (2.9)	33.2 (3)	34.2 (3.2)	33.8 (3.1)	33.3 (3)
Current BMI, kg/m^2	23.5 (4.3)	23.6 (4.5)	24.3 (5.1)	26.2 (6.9)	23.7 (4.7)	23.5 (4.3)	24.4 (5.3)
White, %	93.1	92.7	87.8	93.4	91.4	93.2	91.8
Family history of diabetes, %	19.3	21.1	23.6	26.8	19.7	20.3	21.1
Ever or currently married, %	94.1	93.3	94.8	95.6	91.1	94.0	95.1
Parity	1.3 (1.2)	1.3 (1.2)	1.2 (1)	1.2 (1.2)	1.1 (1.1)	1.2 (1.2)	1.3 (1.2)
Alcohol consumption, g/day	3.1 (5.3)	3 (5.3)	2.4 (3.7)	2.7 (5.1)	3.2 (6)	3.1 (5.3)	2.7 (4.6)
Never smoked, %	28.7	28.8	22.7	26.5	31.4	28.7	25.5
Total energy intake, kJ/day	7683.9 (2299.5)	7752.1 (2356.8)	7591.0 (2198.3)	7739.1 (2270.6)	7539.6 (2317.9)	7703.6 (2317.1)	7744.6 (2274.0)
AHEI score	48.3 (10.7)	47.5 (11)	47.5 (10.5)	47.7 (11.1)	48.6 (11)	48.1 (10.8)	47.5 (10.7)
Physical activity, h/week	3 (4.4)	2.9 (4.5)	2.5 (4)	2.7 (5)	3 (4.6)	3 (4.5)	2.7 (4.2)

Values are means (SD) for continuous variables and percentages for categorical variables and are standardised to the age distribution of the study population

[a] Age-standardised characteristics of OC users are not shown (*n* = 2551)

[b] Value is not age adjusted

their menstrual cycles were always irregular during mid-adulthood showed 112% (95% CI 56, 190%) higher risk of GDM than the women reporting very regular cycles (Fig. 2). The association was attenuated but remained after further adjustment for time-varying diet, alcohol consumption, smoking status and physical activity during follow-up (RR 1.65 [95% CI 1.21, 2.25]). The risk of GDM was also greater among women who reported a long cycle length (≥32 days) during mid-adulthood compared with women with a cycle length of 26–31 days (Fig. 2). In the fully adjusted models, women who reported long cycle length had 42% (95% CI 15, 75%) higher risk of GDM, compared with women reporting a normal cycle length. There was no evidence of interaction between cycle length and regularity on the risk of GDM (Table 2).

We then cross-classified women according to their menstrual cycle characteristics at different age ranges across their reproductive life (Table 3). Women who reported a usual cycle length shorter than 32 days in early adulthood but longer in mid-adulthood were more than twice as likely to experience GDM than women who maintained short cycle length (RR 1.98 [95% CI 1.34, 2.92]). A similar pattern was observed for women whose cycles changed from regular early in their reproductive years to irregular in mid-adulthood (Table 3).

The associations between menstrual cycle characteristics during mid-adulthood and GDM risk across strata of BMI at age 18 years and 1993 are depicted in Table 4. There was no evidence of any significant differences in these relations across strata of BMI. Similarly, we found no evidence that the relations between cycle characteristics and GDM differed according to time-varying BMI, diet quality, smoking, physical activity, age, parity or infertility history (ESM Table 2).

Last, we conducted a series of sensitivity analyses to evaluate the robustness of the associations between menstrual cycle characteristics and the risk of GDM. The findings were similar when we included women who provided partial data on menstrual cycle characteristics during adolescence, early adulthood and mid-adulthood (ESM Table 3), when we included pregnancies reported before 1993 (ESM Table 4), and when we excluded women reporting a GDM diagnosis before 1993 (ESM Table 5). The associations of irregular and long menstrual cycle during mid-adulthood with the risk of GDM also persisted when we excluded women who were older than 40 years in 1993 or those who reported 'no period' or '>50 days or too irregular to estimate', when we excluded participants with hirsutism, endometriosis, uterine fibroids or multiple births, and when our analysis was restricted to White women (ESM Table 6).

Discussion

Results from this large prospective cohort revealed that pre-pregnancy irregular and long menstrual cycles during mid-adulthood were associated with a greater risk of GDM, especially for women who converted from short or regular cycles in adolescence or young adulthood to long or irregular patterns in mid-adulthood. These relations were independent of the BMI determined across the reproductive lifespan, as well as other well known risk factors for GDM such as

Menstrual cycle characteristics	GDM/pregnancies	Multivariable models[a] RRs (95% CIs)	Multivariable models[a] RRs (95% CIs)	Multivariable models[a] *p* value	Further adjusting for lifestyle factors[b] RRs (95% CIs)	Further adjusting for lifestyle factors[b] RRs (95% CIs)	Further adjusting for lifestyle factors[b] *p* value
Cycle regularity							
14–17 years							
OC user	72/1455	1.30 (0.99, 1.71)		0.06	1.25 (0.95, 1.64)		0.11
Very regular	164/4390	1 [Reference]		NA	1 [Reference]		NA
Regular	176/4498	1.05 (0.85, 1.29)		0.66	1.10 (0.89, 1.35)		0.37
Usually irregular	85/2260	1.03 (0.79, 1.33)		0.85	1.07 (0.83, 1.38)		0.61
Always irregular or no period	81/1815	1.16 (0.90, 1.51)		0.25	1.15 (0.89, 1.49)		0.28
18–22 years							
OC user	313/7383	1.16 (0.93, 1.45)		0.19	1.17 (0.94, 1.46)		0.17
Very regular	101/2666	1 [Reference]		NA	1 [Reference]		NA
Regular	85/2429	0.90 (0.68, 1.19)		0.45	0.93 (0.70, 1.23)		0.60
Usually irregular	45/1202	0.99 (0.70, 1.39)		0.94	1.04 (0.74, 1.47)		0.81
Always irregular or no period	34/738	1.11 (0.76, 1.62)		0.58	1.10 (0.76, 1.60)		0.62
29–46 years							
OC user	151/3521	1.16 (0.95, 1.42)		0.14	1.16 (0.96, 1.42)		0.13
Very regular	260/7030	1 [Reference]		NA	1 [Reference]		NA
Regular	102/2678	1.03 (0.83, 1.29)		0.77	1.02 (0.81, 1.27)		0.89
Usually irregular	24/690	0.94 (0.62, 1.43)		0.79	0.89 (0.59, 1.34)		0.57
Always irregular or no period	41/499	2.12 (1.56, 2.90)		<0.001	1.65 (1.21, 2.25)		0.002
Cycle length (days)							
18–22 years							
OC user	313/7383	1.19 (0.99, 1.43)		0.07	1.18 (0.98, 1.43)		0.08
≤25	22/634	0.90 (0.58, 1.40)		0.64	0.96 (0.62, 1.49)		NA
26–31	163/4357	1 [Reference]		NA	1 [Reference]		0.86
≥32 or too irregular to estimate	80/2044	1.03 (0.79, 1.33)		0.85	1.02 (0.79, 1.33)		0.85
29–46 years							
OC user	151/3521	1.26 (1.04, 1.54)		0.02	1.27 (1.04, 1.54)		0.02
≤25	46/930	1.38 (1.01, 1.87)		0.04	1.34 (0.99, 1.82)		0.06
26–31	257/7531	1 [Reference]		NA	1 [Reference]		NA
≥32 or too irregular to estimate	124/2436	1.55 (1.26, 1.92)		<0.001	1.42 (1.15, 1.75)		0.001

Fig. 2 Adjusted RRs (95% CI) for incidence of GDM according to menstrual cycle regularity and length during adolescence (age 14–17 years), early adulthood (age 18–22 years) and mid-adulthood (age 29–46 years) among 10,906 premenopausal women who contributed 14,418 pregnancies from the NHS II (1993–2009). [a]Multivariable model was adjusted for age (continuous), age at menarche (continuous), BMI at age 18 years (continuous), ethnicity (White or other), family history of diabetes (yes or no) and parity (1, 2, 3 or ≥4). [b]Based on multivariable model with additional adjustment for time-varying alcohol consumption (0, 0.1–5.0 or ≥5.1 g/day), BMI (<23, 23–24.9, 25–29.9, 30–34.9 or ≥35 kg/m^2), physical activity (<150 or ≥150 min/week), smoking status (never, past or current) and AHEI 2010 score (below or above median) during follow-up. NA, not applicable

advanced maternal age, greater parity and unhealthy lifestyles. Cycle characteristics in adolescence and early adulthood were not associated with GDM.

Irregular and long menstrual cycles have been associated with a greater risk of insulin resistance and type 2 diabetes [8–10]. Polycystic ovary syndrome, a condition commonly characterised by menstrual dysfunction including long or irregular cycles, was also associated with an increased prevalence of GDM [25]. Evidence linking menstrual cycle characteristics and GDM, however, is scant and inconsistent. In a small case–control study conducted among 170 American women, Haver and colleagues reported that irregular menstrual cycle was more prevalent among women with GDM than the comparison group (24% vs 7%) [11]. In a recent prospective cohort conducted among 3490 Swedish women, Dishi and colleagues reported that irregular cycle was unrelated to GDM [12]; instead, they found a greater risk of GDM among women reporting long menstrual cycles (>36 days) compared with women reporting cycles between 25 and 30 days (OR 1.6 [95% CI 0.98, 2.67]). Inferences of findings from these studies were hindered by several potential methodological limitations. Our study was able to improve upon these studies as a result of our larger sample size, prospective design, finer characterisation of menstrual cycle characteristics at multiple time points, and detailed data on important covariates (e.g., OC use, BMI and lifestyle factors).

Our findings extend and refine the existing evidence in this area. Because OCs affect cycle characteristics and are often

Table 2 Adjusted RRs (95% CI) for incidence of GDM according to joint categories of menstrual cycle regularity and length in early adulthood (age 18–22 years) and mid-adulthood (age 29–46 years) (NHS II, 1993–2009)

Cycle regularity	Cycle length	GDM/pregnancies	RRs (95% CI)	
			Multivariable adjusted[a]	Further adjustment for lifestyle factors[b]
18–22 years				
OC users	OC users	313/7383	1.18 (0.98, 1.42)	1.17 (0.97, 1.41)
Very regular or regular	<32 days	168/4438	1.00 (reference)	1.00 (reference)
Very regular or regular	≥32 days	18/657	0.72 (0.45, 1.17)	0.74 (0.46, 1.20)
Irregular or no cycles	<32 days	17/553	0.80 (0.49, 1.30)	0.87 (0.53, 1.42)
Irregular or no cycles	≥32 days	62/1387	1.15 (0.87, 1.53)	1.14 (0.86, 1.51)
p for interaction[c]			0.06	0.13
29–46 years				
OC users	OC users	151/3521	1.23 (1.01, 1.50)	1.24 (1.02, 1.50)
Very regular or regular	<32 days	290/8256	1.00 (reference)	1.00 (reference)
Very regular or regular	≥32 days	72/1452	1.52 (1.18, 1.95)	1.45 (1.13, 1.87)
Irregular or no cycles	<32 days	13/205	1.69 (0.98, 2.91)	1.50 (0.87, 2.57)
Irregular or no cycles	≥32 days	52/984	1.51 (1.14, 2.02)	1.30 (0.98, 1.73)
p for interaction[c]			0.12	0.11

[a] Multivariable model was adjusted for age (continuous), age at menarche (continuous), BMI at age 18 years (continuous), ethnicity (White or others), family history of diabetes (yes or no) and parity (1, 2, 3 or ≥4)

[b] Based on multivariable model with additional adjustment for time-varying alcohol consumption (0, 0.1–5.0 or ≥5.1 g/day), BMI (<23, 23–24.9, 25–29.9, 30–34.9 or ≥35 kg/m^2), physical activity (<150 or ≥150 min/week), smoking status (never, past or current) and AHEI 2010 score (below or above median) during follow-up

[c] *p* for interaction as tested by excluding women reporting OC use

used to treat women presenting with menstrual cycle disorders, it is important to eliminate the 'noise' of OC use at the time of menstrual cycle characteristic assessment. In this study, we categorised women who used OCs as a separate exposure group, which allowed us to obtain estimates that were independent of OC use. Besides, while it is abundantly clear that obesity, unhealthy lifestyles, advanced age and greater parity are important risk factors for GDM [26], no studies have evaluated whether the association between menstrual cycle dysfunction and GDM was modified by these risk factors. The absence of effect modification by BMI, unhealthy lifestyles, advanced age, greater parity and infertility history suggests that menstrual cycle characteristics might be independent risk factors for GDM. We also noted that the relations of long and irregular menstrual cycles with greater GDM risk persisted when we excluded women with hirsutism, endometriosis or uterine fibroids, indicating that these relations were not solely driven by polycystic ovary syndrome or other common gynaecologic conditions. Finally, in contrast to previous studies that retrospectively assessed menstrual cycle characteristics at one point in time, we collected cycle characteristics at three different time points across women's reproductive lifespan. Interestingly, we found that the risk of GDM was greater among women who converted from initial short or regular cycles to long or irregular patterns compared with women maintaining short or regular cycles across their reproductive lifespan. These findings suggested that the transition from healthy to unhealthy cycle phenotypes might be a surrogate of metabolic changes (e.g., insulin resistance) that play a critical role in the development of GDM.

Irregular and long menstrual cycles could be indicators of unfavourable hormonal and metabolic phenotypes that have been implicated in the aetiology of GDM. The disrupted hormonal environment is hypothesised to play a critical role in the association between menstrual cycle dysfunction and incident GDM. Irregular and long menstrual cycles are strongly associated with hyperinsulinaemia [27], which can inhibit the production of sex hormone-binding globulin and consequently higher levels of free testosterone [28], both of which are known as risk factors for GDM and type 2 diabetes [29–32]. Besides the disrupted hormonal environment, irregular and long menstrual cycles have been associated with underlying lipid metabolism and metabolic disorders (e.g., insulin resistance) [33–35], which may also be involved in the development of GDM [36]. Previous studies have documented that women with polycystic ovary syndrome, for whom ovarian dysfunction – including long or irregular cycles – and excess androgens are distinctive clinical features, have hyperinsulinism, insulin resistance and lipid metabolic disorders [37, 38].

The strengths of this study include its large sample size, prospective design with a long-term follow-up, a high response rate of each follow-up cycle, availability of menstrual cycle characteristics across the reproductive lifespan, and comprehensive

Table 3 Adjusted RRs (95% CI) for incidence of GDM according to changes in menstrual cycle characteristics among 10,906 premenopausal women who contributed 14,418 pregnancies from the NHS II (1993–2009)

Changes in menstrual cycle characteristics	GDM/pregnancies	RRs (95% CI)	
		Multivariable models[a]	Final models adjusted for lifestyle factors[b]
Change in regularity from age 14–17 to 29–46 years			
Maintaining regular	234/6493	1.00 (reference)	1.00 (reference)
Regular to irregular	18/268	1.70 (1.07, 2.72)	1.43 (0.89, 2.29)
Irregular to regular	83/2287	1.02 (0.79, 1.30)	1.02 (0.80, 1.31)
Irregular maintained	38/787	1.36 (0.98, 1.89)	1.21 (0.87, 1.67)
OC user	205/4583	1.24 (1.03, 1.49)	1.21 (1.01, 1.46)
Change in regularity from age 18–22 to 29–46 years			
Maintaining regular	142/3912	1.00 (reference)	1.00 (reference)
Regular to irregular	12/145	1.96 (1.10, 3.49)	1.68 (0.93, 3.01)
Irregular to regular	37/1104	0.92 (0.64, 1.31)	0.94 (0.66, 1.35)
Irregular maintained	22/445	1.33 (0.86, 2.04)	1.20 (0.78, 1.83)
OC user	365/8812	1.18 (0.98, 1.43)	1.17 (0.96, 1.42)
Change in length from age 18–22 to 29–46 years			
Maintaining <32 days	123/3558	1.00 (reference)	1.00 (reference)
<32 to ≥32 days	28/408	2.13 (1.44, 3.16)	1.98 (1.34, 2.92)
≥32 to <32 days	29/774	1.08 (0.73, 1.61)	1.10 (0.73, 1.63)
≥32 days maintained	33/866	1.11 (0.77, 1.62)	1.04 (0.71, 1.50)
OC user	365/8812	1.26 (1.03, 1.54)	1.24 (1.01, 1.52)

[a] Multivariable model was adjusted for age (continuous), age at menarche (continuous), BMI at age 18 years (continuous), ethnicity (White or others), family history of diabetes (yes or no) and parity (1, 2, 3 or ≥4)

[b] Based on multivariable model with additional adjustment for time-varying alcohol consumption (0, 0.1–5.0 or ≥5.1 g/day), BMI (<23, 23–24.9, 25–29.9, 30–34.9 or ≥35 kg/m^2), physical activity (<150 or ≥150 min/week), smoking status (never, past or current) and AHEI 2010 score (below or above median) during follow-up

measurements of important confounding factors. Our study also has some limitations. First, measurement error in self-reported menstrual cycle characteristics is inevitable, though previous studies have documented the validity of self-reported menstrual cycle characteristics [7, 16]. In this case, however, exposure misclassification is suspected to be non-differential with respect

Table 4 Adjusted RRs (95% CI) for incidence of GDM in relation to irregular and long menstrual cycles in mid-adulthood (age 29–46 years), stratified by BMI at age 18 years and in 1993 (NHS II, 1993–2009)

	BMI at age 18 years[a] (RRs 95% CI)		BMI in 1993[b] (RRs 95% CI)	
	<25 kg/m^2 (GDM=502)	≥25 kg/m^2 (GDM=76)	<25 kg/m^2 (GDM=305)	≥25 kg/m^2 (GDM=273)
Regularity				
OC user	1.09 (0.88, 1.35)	1.60 (0.93, 2.75)	1.18 (0.90, 1.54)	1.20 (0.89, 1.62)
Very regular	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Regular	1.01 (0.80, 1.28)	0.99 (0.47, 2.07)	0.92 (0.67, 1.26)	1.09 (0.79, 1.51)
Usually irregular	0.83 (0.52, 1.32)	1.30 (0.51, 3.29)	0.67 (0.34, 1.32)	1.12 (0.65, 1.91)
Always irregular/no period	1.61 (1.13, 2.30)	1.97 (1.03, 3.76)	1.70 (1.01, 2.86)	1.84 (1.25, 2.70)
p for interaction[c]	0.19		0.29	
Length (days)				
OC users	1.18 (0.95, 1.46)	1.85 (1.06, 3.24)	1.37 (1.05, 1.80)	1.21 (0.90, 1.63)
≤25	1.30 (0.94, 1.80)	1.67 (0.69, 4.06)	1.52 (1.02, 2.28)	1.18 (0.75, 1.88)
26–31	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥32 or too irregular to estimate	1.37 (1.09, 1.72)	1.91 (1.08, 3.35)	1.52 (1.11, 2.07)	1.36 (1.02, 1.81)
p for interaction[c]	0.41		0.86	

[a] Multivariable model was adjusted for age (continuous), age at menarche (continuous), ethnicity (White or others), family history of diabetes (yes or no) and parity (1, 2, 3 or ≥4), as well as time-varying alcohol consumption (0, 0.1–5.0 or ≥5.1 g/day), BMI (<23, 23–24.9, 25–29.9, 30–34.9 or ≥35 kg/m^2), physical activity (<150 or ≥150 min/week), smoking status (never, past or current) and AHEI 2010 score (below or above median) during follow-up

[b] Multivariable model was adjusted for age (continuous), age at menarche (continuous), BMI at age 18 years (continuous), ethnicity (White or others), family history of diabetes (yes or no) and parity (1, 2, 3 or ≥4), as well as time-varying alcohol consumption (0, 0.1–5.0 or ≥5.1 g/day), physical activity (<150 or ≥150 min/week), smoking status (never, past or current) and AHEI 2010 score (below or above median) during follow-up

[c] *p* for interaction as tested by excluding women reporting OC use

to incident GDM, potentially biasing estimations towards the null. Second, incident GDM diagnosis was self-reported through the biennial questionnaires. However, a high degree of accuracy of self-reported GDM against medical record review has been confirmed among a subgroup of participants from this cohort [17]. Further, the overall rate of GDM in our present study (4.0%; 578 cases of 14,418 pregnancies) fell within the range of the estimated GDM prevalence in the USA during a similar period (3–6%) [3]. Third, we used the National Diabetes Data Group criteria for GDM diagnosis, which may have resulted in a reduced risk estimation given that more women with mild hyperglycaemia would be diagnosed with GDM based on the Carpenter and Coustan criteria or the International Association of Diabetes and Pregnancy Study Group approach [39]. Fourth, our study participants were mostly White (>95%) and shared a common profession and educational qualification, which may restrict the generalisability of our results. Therefore, further studies involving women of other ethnicity or race with more diverse socioeconomic status are warranted to verify our findings. Finally, although we accounted for various potential confounders (e.g., demographic and reproductive characteristics, BMI at age 18 years and lifestyle factors), residual confounding from unadjusted covariates such as diet quality during pregnancy cannot be fully ruled out.

In conclusion, based on this large prospective cohort, women whose cycles were long (≥32 days) or irregular during mid-adulthood were at an elevated risk of GDM. These relationships appeared to be independent of other commonly recognised risk factors for GDM. Our results suggest that menstrual cycle characteristics before pregnancy may serve as early markers for subsequent risk of GDM.

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Data availability Data described in the manuscript, code book and analytic code will not be made publicly available. Further information including the procedures for obtaining and accessing data from NHS II is described at https://www.nurseshealthstudy.org/researchers (email: nhsaccess@channing.harvard.edu). Questionnaires are publicly available at: https://nurseshealthstudy.org/participants/questionnaires.

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