Published in final edited form as:

Fertil Steril. 2011 July ; 96(1): 236–240.e1. doi:10.1016/j.fertnstert.2011.04.005.

Ramifications of adolescent menstrual cycles ≥ 42 days in young adults

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Abstract

Objective—To determine to what degree annual reports from ages 14 to 19 years of menstrual cycles ≥ 42 days would be associated with increased body mass index (BMI), waist circumference, glucose, insulin, and homeostasis model assessment insulin resistance (HOMA-IR) at ages 14–25 years.

Design—Prospective 11-year follow-up from ages 14 to 25 years.

Setting—Urban-suburban schools, post-high school.

Patient(s)—A total of 370 schoolgirls.

Intervention(s)—None.

Main Outcome Measure(s)—BMI, waist, insulin, glucose, HOMA-IR.

Result(s)—From ages 14 to 19 years, 269 girls had 0/6 annual reports of menstrual cycles ≥ 42 days, 74 had 1, 19 had 2, and 8 had ≥ 3 . Among these four categories, girls with ≥ 3 annual reports had highest free T and DHEAS at age 14, highest BMI and waist at ages 14, 19, and 25, highest insulin at age 25, and highest glucose and HOMA-IR at age 24 years. The number of annual reports of menstrual cycles ≥ 42 days was positively related to change in BMI and waist and inversely with change in high-density lipoprotein cholesterol from ages 14 to 25 years.

Conclusion(s)—Three or more annual reports of menstrual cycles ≥ 42 days during ages 14–19 are associated with high BMI, waist circumference, insulin, glucose, and HOMA-IR at ages 14–25 years. (*Fertil Steril*® 2011;96: 236–40).

Keywords

Adolescence; menstrual cycle; free testosterone; BMI; centripetal obesity; insulin; HOMA insulin resistance

Women with a history of irregular menstrual cycles have increased risk of coronary heart disease (1, 2) and type 2 diabetes (T2DM) compared to women with regular cycles (27–29 days) (3, 4). Determining the degree of menstrual cycle irregularity in adult women is a simple clinical parameter which is a valuable instrument to estimate the degree of metabolic and endocrine disorders (5, 6). Within this frame of reference (1–3), we determined whether and to what degree annual reports of menstrual cycles ≥ 42 days during ages 14–19 years would be associated with obesity and endocrinopathy at 25 years of age.

Materials and Methods

Study Population

In 1987, the National Heart, Lung, and Blood Institute (NHLBI) initiated a 10-year longitudinal multicenter study (the NHLBI Growth and Health Study [NGHS]) to investigate the development of obesity in black and white girls during adolescence and its environmental, psychosocial, and cardiovascular disease risk factor correlates (7–9). Participant eligibility was limited to girls who declared themselves as being either black or white and who lived in racially concordant households. Annual visits were carried out from 9–10 through 18–19 years of age. The follow-up rate was 89% at the tenth annual visit. After the completion of the NGHS, the Cincinnati Clinic carried out investigator-initiated studies for 5 more years, measuring fasting insulin at ages 20–25 and fasting glucose at ages 20–24 years, thus providing up to 15 years of follow-up.

All clinical assessments were conducted using a common protocol by centrally trained staff. In ancillary projects, the Cincinnati Clinic measured fasting insulin at baseline (mean age 10 years) and at mean age 16 years and sex steroid hormones and SHBG at mean ages 10, 12, and 14 years, in addition to the NGHS variables: lipid profiles, glucose, apolipoprotein A1, and systolic and diastolic blood pressures. Sexual maturation was assessed by trained staff. The onset of menarche was ascertained annually by interview by trained pediatric nurse practitioners (10). At each annual NGHS visit, from ages 10 to 19, information was obtained from postmenarchal participants on the number of days since the previous menstrual cycle and whether they were pregnant. Annual reports of menstrual cycles ≥ 42 days from ages 14 to 19 were used to identify cases to allow comparison with van Hooff et al. (11, 12) and Chiazze et al. (13). Defining oligomenorrhea in 15-year-old white Dutch girls by menses ≥ 42 days, van Hooff et al. reported that oligomenorrheic girls were more likely than girls with either irregular or normal menses to be hyperandrogenemic and to have polycystic ovaries (11, 12). Chiazze et al. reported that only 2.5% of 15–19-year-old girls had average menstrual cycle lengths ≥ 40 days (13).

In the NGHS cohort, 493 Cincinnati girls had measures of sex hormones at age 14, 427 had annual reports on menstrual cycles at age 14, and 370 had at least five annual reports on menstrual cycles from ages 14 to 19 years. In the present study, focused on these 370 girls, we prospectively assessed relationships of annual reports of menstrual cycles ≥ 42 days from ages 14 to 19 with obesity and endocrinopathy at age 25, using insulin, glucose, insulin resistance (IR), body mass index (BMI), and waist circumference as outcome variables.

IRB Approval

In the NGHS and the 5-year extension study (10), the procedures followed were in accordance with the ethical standards of the Institutional Review Boards of the centers, who approved the study. Signed informed consent was obtained from each of the girls' parent(s) or guardian(s) and assent from the girls in the NGHS, and signed consent from each of the participants (now adult women) was obtained in the extension study.

Laboratory and Clinical Measurements

Methods for measurement of SHBG, E₂, DHEAS, free T, lipids, apolipoprotein A1, fasting glucose, fasting serum insulin, height, weight, waist circumference, and systolic and diastolic blood pressures have been previously described (8). Blood was drawn after an overnight fast with participants in the seated position. Blood drawing was not scheduled by menstrual status or day of menstrual period. The NGHS used BMI to assess overweight (14–16) annually (8) and waist circumference as an indicator of fat patterning.

NGHS subjects having fasting blood glucose ≥ 126 mg/dL (17) at age 10 and/or type 1 diabetes mellitus based on patient-physician records at any time from age 10 through 24 were excluded ($n = 7$) from the analysis sample for this report (18). Diagnosis of type 1 diabetes was based on World Health Organization criteria, fasting glucose ≥ 126 mg/dL, and self-reported diabetes with treatment by a physician (17). We did not have measurement of C-peptides or diabetes autoantibody levels, criterion standard methods (19) to optimally distinguish type 1 from type 2 diabetes. There were no other exclusion criteria.

After an overnight fast (≥ 8 hours), childhood insulin levels were measured at age 10 by the Michigan Diabetes Research and Training Center (Ann Arbor) and at ages 16–25 by the Endocrine Lab (Children's Hospital Medical Center) by competitive protein-binding radioimmunoassays. Because outcomes were virtually the same whether or not insulin levels were transformed into Z-scores (data not shown), only insulin data is displayed. Of the reported 370 girls, 249 had insulin first measured at age 10 and another 90 girls had insulin first measured at age 16. We denoted the first insulin measure at either age 10 or 16 as “childhood insulin.” We used fasting insulin as an indicator of IR based on reports by Huang et al. (20) and Schwartz et al. (21). We also measured homeostasis model assessment IR (HOMA-IR) (22).

Menstrual categories were based on the number of annual reports of delayed menstrual cyclicity (≥ 42 days since the last menses cycle) (11) in 6 annual reports from ages 14 to 19 years (Figs. 1–3; Supplemental Table 1 [available online at <http://www.fertstert.org>]). Categories of annual reports of menstrual cycles ≥ 42 days were 0 (none reported), 1 (one reported), 2 (two reported), and 3 (≥ 3 reported) (Supplemental Table 1; Figs. 1–3).

Statistical Methods

Baseline demographic data (mean $\pm$ SD) are summarized in Supplemental Table 1 for girls aged 14–19 years categorized by the number of annual reports of menstrual cycles ≥ 42 days.

Separated by menstrual categories and after adjustment by race, least-square means were compared and the Hochberg-Benjamini method controlling for discovery rate ($P \leq .05$) used for multiple comparisons among the four menses categories for each outcome measure (Figs. 1–3).

Correlations (Spearman) were calculated between the number of annual reports of menstrual cycles ≥ 42 days (0–6) from ages 14 to 19 and changes from ages 14 to 25 in body weight, waist circumference, BMI, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol and triglyceride, insulin (from childhood to age 25), and glucose and IR (from ages 10 to 24). Only significant correlations are presented in Table 1.

Stepwise regression was carried out with the dependent variables being changes from ages 14 to 25 in body weight, waist circumference, BMI, and HDL and explanatory variables, including race, age of menarche, duration of follow-up, and the number of annual reports of menstrual cycles ≥ 42 days (0 to 6) from ages 14 to 19 (Table 1).

The relationship between age of menarche and the number of annual reports of menstrual cycles ≥ 2 days (0 to 6) from ages 14 to 19 was assessed by the Mantel-Haenszel test.

Stepwise logistic regression was used with the dependent variable being 0 or ≥ 1 annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 and the explanatory variables being race, change in BMI from ages 14 to 19, and age of menarche.

Results

From ages 14 to 19 years, 269 girls had 0 annual reports of delayed menstrual cycles ≥ 2 days, and 101 had ≥ 1 annual reports of cycles ≥ 2 days, with no reported pregnancies at the annual visit interview accounting for the cycles ≥ 2 days. Of these 101 girls, 74 had 1 annual report of menstrual cycles ≥ 2 days, 19 had 2, and 8 had ≥ 3 (Supplemental Table 1; Figs. 1–3). Of the 19 girls with two annual reports of cycles ≥ 2 days, in 12 the reports were sequential, three first reported cycles ≥ 2 days at age 14, one at age 15, five at age 17, and three at age 18. Of the eight girls with ≥ 3 menstrual cycles ≥ 2 days, all of the reports were sequential, 5 first reported cycles ≥ 2 days at age 14, two at age 15, and one at age 16.

At age 14, when categorized by number of annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 (0, 1, 2, or ≥ 3), free T and DHEAS were highest in girls with ≥ 3 annual reports (Fig. 1). At age 14, E₂ and SHBG did not differ between groups categorized by number of annual reports from ages 14 to 19 (data not shown).

There was no association between age at menarche and the number of annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 (Mantel-Haenszel: $\chi^2 = 0.009$; $P = .92$).

At ages 14, 19, and 25 years, BMI and waist circumference were much higher in girls with ≥ 3 annual reports of menstrual cycles ≥ 2 days than in girls with 0, 1, or 2 annual reports (Fig. 2).

Glucose and HOMA-IR at age 24 and insulin at age 25 were much higher in girls with ≥ 3 annual reports of menstrual cycles ≥ 2 days than in girls with 0, 1, or 2 annual reports (Fig. 3).

HDLC and LDLC did not differ ($P > .05$) between groups categorized by number of annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 (data not shown).

In the total analysis cohort ($n = 370$), the number of annual reports of menstrual cycles ≥ 2 days (0 to 6) from ages 14 to 19 was positively correlated with age 14 to 19 increases in body weight, waist circumference, and BMI and inversely correlated with HDLC change (Table 1). There were no other significant correlations ($P > .4$) between the number of annual reports of menstrual cycles ≥ 2 days and changes in LDLC and triglycerides (from ages 14 to 25), insulin (from childhood to age 25), and glucose and IR (from ages 10 to 24) (data not shown).

By stepwise regression, the number of annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 years was a significant positive explanatory variable (along with race) for body weight, waist circumference, and BMI change from ages 14 to 25 years and was a significant negative explanatory variable (along with race) for change in HDLC (Table 1). Age of menarche was inversely related to change in waist circumference (Table 1).

Change in BMI from ages 14 to 19 was a significant explanatory variable for ≥ 1 annual report of menstrual cycles ≥ 2 days (odds ratio 1.139, 95% confidence interval 1.067–1.215; $P < .0001$).

Discussion

The present study had three novel central findings. First, when categorized by number of annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 years, BMI, waist circumference (at ages 14, 19, and 25), and insulin (at age 25) were highest in girls with ≥ 3 annual reports, as were glucose and HOMA-IR at age 24. Menstrual cycles ≥ 2 days were predominantly sequential, starting mostly in the early years since menarche (ages 14–16) rather than later. Moreover, Of the eight girls with ≥ 3 menstrual cycles ≥ 2 days, all of the reports were sequential, five first reported cycles ≥ 2 days at age 14, two at age 15, and 1 at age 16.

Second, the number of annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 years were positive significant explanatory variables for change in body weight, waist circumference, and BMI from ages 14 to 25, along with race, and were negatively associated with change in HDLC from ages 14 to 25. A caveat is that the regression model reveals associations but does not prove causality. Third, at age 14, free T and DHEAS were highest in girls with ≥ 3 annual reports of menstrual cycles ≥ 2 days during ages 14–19 years.

A limitation of the study is that the annual report of delayed menses does not fully disclose what is going on during the rest of the year (i.e., oligomenorrhea, amenorrhea, a single episode, etc.). However, by obtaining annual reports from ages 14 through 19, a pattern of menses delays over a 6-year period should provide a more reliable estimate of menses delays. A second limitation of the present report is the fact that annual reports of menstrual cyclicity ≥ 2 days were determined from answers to the question, “When did your last menstrual period begin?” Although this question was asked of postmenarchal participants at every annual clinic visit, it would have been possible for a participant to be scheduled within 30 days of her last period each year, despite having had extended menstrual cycles every year. However, this means that the group reporting no extended cycles would have included false negatives, which indicates that our finding may be conservative.

Basal fasting insulin has been shown in 24-year prospective follow-up to be the most important explanatory variable for the development of dysglycemia (23). In the present study, by virtue of its independent and significant association with young adult insulin, glucose, and HOMA-IR, the documentation of the presence of ≥ 3 annual reports of menstrual cycles ≥ 2 days from ages 14 to 19 years should facilitate primary prevention of T2DM by diet, exercise, weight loss or minimizing weight gain (24), and metformin (25).

As is the case in adult women (3), recording the degree of menstrual cycle irregularity from ages 14–19 is a simple clinical parameter that appears to be valuable in estimation of insulin, glucose, and HOMA-IR, integral to the development of impaired fasting glucose and T2DM in young adulthood (10, 26).

In the present study, the association of high free T and DHEAS at age 14 with ≥ 3 annual reports of menstrual cycles ≥ 2 days between ages 14 and 19 may foretell findings in postmenopausal women, where a history of irregular menses and elevated androgens is associated with high risk for worsening cardiovascular event-free survival (27). Age-adjusted risk for coronary heart disease mortality also increases in women with irregular menstrual cycles (28).

In the present study, change in BMI from ages 14 to 19 was a significant independent correlate of ≥ 1 annual report of menstrual cycles ≥ 2 days, congruent with the report by de Pergola et al. (29) that “more than 20% of women with simple obesity have oligomenorrhea” and “central fat accumulation seems to have a possible direct role in this menstrual alteration, independently of hyperinsulinemia and/or insulin resistance.”

The constellation of obesity, centripetal obesity, hyperinsulinemia, IR, and hyperandrogenemia, most marked in girls in the present study with 3 annual reports of menstrual cycles 42 days during ages 14–19, suggests an underlying presence of polycystic ovary syndrome (PCOS) (30–33). PCOS, in turn, is associated with IR, hyperinsulinemia, and T2DM (30–33). Hyperandrogenemic PCOS phenotypes have the greatest degree of IR and inflammation (34). The presence of 3 annual reports of menstrual cycles 42 days during ages 14–19 years should focus diagnostic attention on hyperandrogenemia, hyperinsulinemia, and PCOS (30, 31, 35), with a goal of exercise/diet (36) and insulin sensitizers (30–32, 37) to reduce hyperinsulinemia and hyperandrogenemia, and with an ultimate goal of primary prevention of T2DM, coronary heart disease (1, 2), and morbid obesity, all of which are associated with PCOS in adult women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported in part by National Institutes of Health grants HL55025, HL48941, HL52911, and HL66430 (J.A.M., S.D.) and the Lipoprotein

Research Fund of the Jewish Hospital of Cincinnati (C.J.G.).

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Figure 1.

Free T and DHEAS at age 14, by categories of age 14–19 annual reports of menstrual cycles ≥ 42 days (0, 1, 2, or 3). Unadjusted mean $\pm$ SD values are displayed. *P* values (analysis of variance adjusting for race): free T: 3 reports .0017 vs. 0, .0069 vs. 1, .0083 vs. 2; DHEAS: 3 reports .0054 vs. 0, .050 vs. 1, .0007 vs. 2; 2 vs. 1.038.

Figure 2.

Body mass index (BMI) and waist circumference at ages 14, 19, and 25 years, by categories of age 14–19 annual reports of menstrual cycles ≥ 42 days (0, 1, 2, or 3). Unadjusted mean $\pm$ SD values are displayed. *P* values (analysis of variance adjusting for race): BMI at age 14: 3 reports .0003 vs. 0, .0015 vs. 1, .0006 vs. 2; BMI at age 19: 3 reports .003 vs. 0, .03 vs. 1; BMI at age 25: 3 reports .0004 vs. 0, .0042 vs. 1, .015 vs. 2; waist circumference at age 14: 3 reports .0002 vs. 0, .0008 vs. 1, .0008 vs. 2; waist circumference at age 19: 3 reports .0005 vs. 0, .007 vs. 1, .02 vs. 2; waist circumference at age 25: 3 reports .0002 vs. 0, .0018 vs. 1, .0079 vs. 2.

Figure 3.

Glucose (at ages 10, 19, and 24), insulin (at ages 10–16, 19, and 25), and homeostasis model assessment insulin resistance (HOMA-IR; at ages 10, 19, and 24) by categories of age 14–19 annual reports of menstrual cycles ≥42 days (0, 1, 2, or 3). Unadjusted mean ± SD values are displayed. *P* values (analysis of variance adjusting for race): glucose at age 24: 3 reports <.0001 vs. 0, <.0001 vs. 1, <.0001 vs. 2; insulin at ages 10–16: 3 reports .047 vs. 0, 1 vs. 0 .026; insulin at age 19: 3 reports .010 vs. 0, 1 vs. 0 .023; insulin at age 25: 3 reports <.0001 vs. 0, <.0001 vs. 1, <.0001 vs. 2; HOMA-IR at age 19: 3 reports .027 vs. 0, 1 vs. 0 .015; HOMA-IR at age 24: 3 reports <.0001 vs. 0, <.0001 vs. 1, <.0001 vs. 2.

Table 1

Significant correlations between the number (0–6) of annual reports of menstrual cycles 42 days (ages 14–19) and changes in body weight, waist circumference, body mass index (BMI), and high-density lipoprotein cholesterol (HDL) during ages 14 to 25 years.

Correlate with annual reports of menstrual cycles 42 d (ages 14–19 y)	n	Mean ± SD	Spearman <i>r</i>	<i>P</i> value
No. of annual reports of menstrual cycles 42 d	370	0.38 ± 0.75		
Body weight change (kg)	361	15.8 ± 12.6	+0.19	.0002
Waist circumference change (cm)	358	9.7 ± 8.8	+0.21	<.0001
BMI change (kg/m ²)	361	5.11 ± 4.55	+0.20	.0001
HDL change (mg/dL)	313	−3.6 ± 9.9	−0.17	.0028

Regression models for changes in body weight, waist circumference, body mass index (BMI), and high-density lipoprotein cholesterol (HDL) from ages 14 to 25 years.

Dependent variable	Significant explanatory variable	Sign	<i>P</i> value	Partial <i>R</i> ²
Body weight change (n = 361)	Race ^a	+	<.0001	7.7%
	No. of annual reports of menstrual cycles 42 d	+	.0031	2.2%
Waist circumference change (n = 358)	Race ^a	+	<.0001	7.0%
	Age of menarche	−	.0008	2.7%
	No. of annual reports of menstrual cycles 42 d	+	.0049	2.1%
BMI change (n = 361)	Race ^a	+	<.0001	9.9%
	No. of annual reports of menstrual cycles 42 d	+	.0024	2.3%
HDL change (n = 313)	Race ^a	−	.0007	4.3%
	No. of annual reports of menstrual cycles 42 d	−	.048	1.2%

Note: Stepwise selection from race, age of menarche, duration of follow-up, and number (0–6) of annual reports of menstrual cycles 42 days from ages 14 to 19.

^aWhite = 1; black = 2.