Ramifications of adolescent menstrual cycles ≥42 days in young adults

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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. ©2011 by American Society for Reproductive Medicine.)

Key Words: 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

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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, E_2, 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 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 ± 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=.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 (HDLC) and low-density lipoprotein (LDLC) 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.

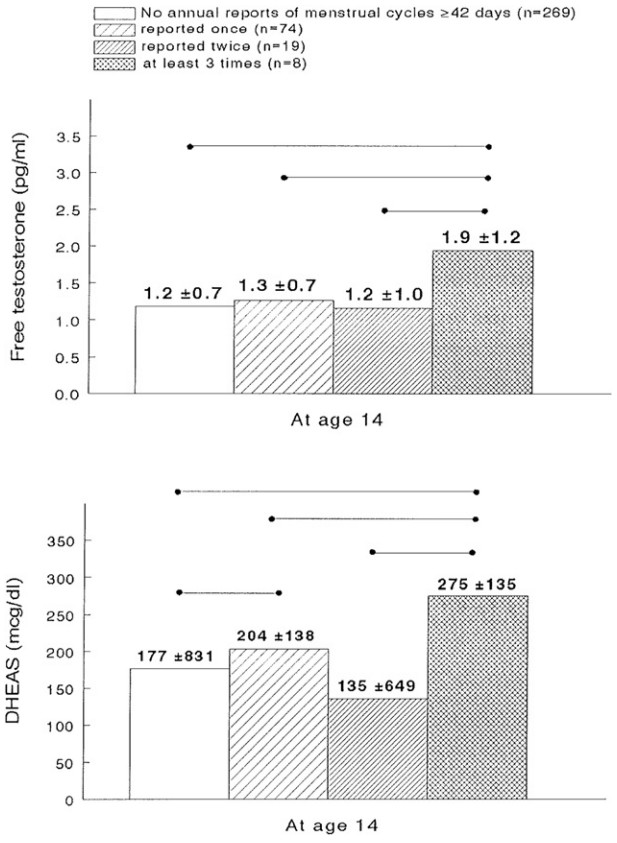
Stepwise regression was carried out with the dependent variables being changes from ages 14 to 25 in body weight, waist circumference, BMI, and HDLC and explanatory variables, including race, age of menarche, duration of follow-up, and the number of annual reports of menstrual cycles ≥42 days (0 to 6)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

The relationship between age of menarche and the number of annual reports of menstrual cycles ≥42 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 ≥42 days from ages 14 to 19 and the explanatory variables being race, change in BMI from ages 14 to 19, and age of menarche.

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 ± 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.



Morrison. Adolescent menstrual cycles ≥42 days. Fertil Steril 2011.

RESULTS

From ages 14 to 19 years, 269 girls had 0 annual reports of delayed menstrual cycles ≥42 days, and 101 had ≥1 annual reports of cycles ≥42 days, with no reported pregnancies at the annual visit interview accounting for the cycles ≥42 days. Of these 101 girls, 74 had 1 annual report of menstrual cycles ≥42 days, 19 had 2, and 8 had ≥3 (Supplemental Table 1; Figs. 1–3). Of the 19 girls with two annual reports of cycles ≥42 days, in 12 the reports were sequential, three first reported cycles ≥42 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 ≥42 days, all of the reports were sequential, 5 first reported cycles ≥42 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 ≥42 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, E_2 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 ≥42 days from ages 14 to 19 (Mantel-Haenszel: $\chi^2 = 0.009$; P=.92).