Menstrual cycle irregularities and their relationship with HbA1c and insulin dose in adolescents with type 1 diabetes mellitus

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Objective: To evaluate the prevalence and risk factors of menstrual cycle irregularities in adolescents with type 1 diabetes mellitus.

Design: Prospective diary of menstrual cycle.

Setting: Pediatric diabetes clinics and nearby schools.

Patient(s): Adolescents with type 1 diabetes mellitus treated with multiple daily insulin doses (n = 56) and 56 healthy adolescents.

Main Outcome Measure(s): Duration and variability of menstrual cycle.

Result(s): Duration of the menstrual cycle was 48 ± 39 and 32 ± 7 days in girls with type 1 diabetes mellitus and controls, respectively. Oligomenorrhea (58.9% vs. 19.6%) and amenorrhea (10.7% vs. 1.8%) were more prevalent in girls with type 1 diabetes mellitus than in controls. Oligomenorrhea was observed in 53.3% of the girls with type 1 diabetes mellitus with optimal metabolic control. Girls with an HbA1c level of 7.6% to 8.9% exhibited increased cycle duration, menstrual cycle variability, and prevalence of oligomenorrhea compared with controls. Regression analysis showed that, for each point of increase in HbA1c, the menstrual cycle duration increased by 5.1 days. Cycle variability was associated with a higher daily insulin dose.

Conclusion(s): Despite optimal metabolic control, a higher prevalence of oligomenorrhea was observed in girls with type 1 diabetes mellitus compared with controls. This is the first report to describe the high variability of the menstrual cycle in type 1 diabetes mellitus. HbA1c and insulin dose are important factors related to menstrual irregularities in type 1 diabetes mellitus. (Fertil Steril® 2010;94:1822–6. ©2010 by American Society for Reproductive Medicine.)

Key Words: Menstrual cycle, menstruation, menses, puberty, type 1 diabetes mellitus, menarche, metabolic control, complications

Several retrospective studies have shown an increased prevalence of menstrual cycle abnormalities in adult women with type 1 diabetes mellitus (1–4), but only a few retrospective studies have evaluated menstrual irregularities in adolescents with type 1 diabetes mellitus (5, 6). These studies have shown that menstrual cycle irregularities are especially prevalent in young women and that these abnormalities decrease with advancing age (1).

Menstrual irregularities in women without diabetes are linked to increased cardiovascular risk, insulin resistance and risk of developing type 2 diabetes in the future (7–9). Menstrual dysfunction in adult women with type 1 diabetes mellitus also has been shown to be a risk factor, independent of metabolic control, of increased cardiovascular risk (4). This evidence makes it especially important to clarify whether menstrual irregularities are present in adolescents with type 1 diabetes mellitus treated with multiple daily insulin injections and their association with metabolic control.

Schroeder et al. (6) evaluated menstrual cycles in type 1 diabetes mellitus and observed that menstrual irregularities increased when HbA1c is >10%. However, the retrospective nature of this study and the heterogeneity of the patients studied leads one to wonder whether some degree of menstrual abnormalities is observed in adolescents treated with multiple daily doses of insulin and who have optimal metabolic control. In addition, the effects of type 1 diabetes mellitus on the variability of menstrual cycle duration have not been evaluated. With the hypothesis that menstrual irregularities still are observed more frequently in adolescents with type 1 diabetes mellitus despite receiving intensive insulin treatment and possessing optimal metabolic control, we conducted a prospective study of menstrual cycles in adolescents with type 1 diabetes mellitus given treatment with at least three daily doses of insulin.

MATERIALS AND METHODS
Subjects

Postmenarchal girls with type 1 diabetes mellitus who were younger than 19 years were matched with healthy control girls on the basis of gynecologic age and body mass index (BMI). Girls with type 1 diabetes mellitus attending three public hospitals in Santiago, Chile, were recruited. Inclusion criteria were severe insulinopenic diabetes treated with insulin from the time of diagnosis. Patients with type 2 or a specific type of diabetes were excluded. All patients were given treatment with at least three daily insulin injections. The degree of metabolic control, however, was not considered as an inclusion or exclusion criterion. Other exclusion criteria were abnormal thyroid levels, presence of other chronic diseases, or treatment with other drugs, including steroids and contraceptive pills.

Healthy girls attending nearby schools were invited to participate in the study. Subjects without chronic conditions who were not receiving contraceptive pills or any other type of medication and who had a normal birth weight and normal age of menarche were included in the study.

Methods

A prospective study of menstrual cycles was performed. Both groups of girls received a calendar to highlight the days of their period. Several measures were taken to ensure the proper fill-out of the diaries. The girls were reminded periodically to fill out their calendars. Girls with type 1 diabetes mellitus were evaluated monthly at the hospital, and the date of their menstrual period was recorded. The control group was contacted by monthly telephone calls, and, to motivate them to complete their calendars, educational activities were performed every 2 months at their school. Prospective diaries have been validated extensively for the evaluation of menstrual cycles (10, 11).

The mean duration of menstrual cycles was obtained for each girl. The variability in menstrual cycles was determined for each girl on the basis of the coefficient of variation (CV) calculated as SD (standard deviation) per mean of cycle duration in each girl divided by 100. Longer menstrual cycles have been described in healthy adolescents (10, 12), and it has been suggested that more stringent criteria be used to diagnose menstrual irregularities (10, 12, 13). According to these data (10, 12, 13), menstrual irregularities were defined as amenorrhea, oligomenorrhea, and polymenorrhea if the cycle duration was >90 days, >45 days, or <25 days, respectively. A normal cycle was defined as a cycle with a duration of 25 to 45 days.

Metabolic control in type 1 diabetes mellitus was classified as optimal, intermediate, or insufficient, according to the International Society of Pediatric and Adolescent Diabetes guidelines (14). The protocol was approved by the Institutional Review Board of the San Borja Arriarán Hospital. Parents provided informed consent, and patients gave their assent before entering the study.

Statistical Analyses

The normality of the variables was assessed with the Kolmogorov-Smirnov test. Cycle duration was not normally distributed and was assessed by using nonparametric statistics. The remaining variables were distributed normally. Differences in continuous variables between the type 1 diabetes mellitus and control groups were compared with use of Student's t-test or Mann-Whitney's U rank test. Differences in proportions of the prevalence of abnormal cycles were evaluated with use of Pearson's χ^2 test.

The characteristics of menstrual cycles among girls with type 1 diabetes mellitus and different degrees of metabolic control was compared with those of control girls by Dunnett's posttest for continuous variables or by logistic regression analysis to compare the prevalence of abnormal cycles. Pearson correlation analysis was performed to evaluate the relationship between continuous variables. Stepwise regression analysis was performed for type 1 diabetes mellitus to evaluate the effect of gynecologic age, metabolic control, and daily insulin dose over the duration of the menstrual cycle and the CV. Body mass index was not included in this analysis because it is associated with insulin dose and metabolic control. Logistic regression analysis was performed to determine the effect of type 1 diabetes mellitus, age of menarche, and other clinical variables on the presence of oligomenorrhea. Data are pre-

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TABLE 1

Clinical and anthropometric characteristics of girls with type 1 diabetes mellitus and control adolescents, as well as metabolic control in patients with type 1 diabetes mellitus.

	Type 1 diabetes mellitus	Control
No.	56	56
Age (y)	15.3 ± 1.7	14.7 ± 1.5[a]
Gynecologic age (mo)	31.7 ± 18.6	27.4 ± 13.3
BMI (kg/m^2)	22.3 ± 2.4	23.2 ± 3.9
Height (cm)	157.9 ± 5.6	158.3 ± 6.3
Waist-to-hip ratio	0.8 ± 0.0	0.9 ± 0.1
Menarche (y)	12.6 ± 1.3	12.1 ± 1.0[a]
Age of onset of type 1 diabetes mellitus (y)	10.0 ± 3.8	
Diabetes mellitus duration (y)	5.4 ± 3.8	
HbA1C (%)	9.5 ± 2.8	
Daily insulin injections (range)	3–7	
Insulin dose (U/kg/d)	1.1 ± 0.4	
Premenarcheal onset (%)	70.9	

Note: Data are presented as the mean ± SD.
[a] $P < .05$, control compared with type 1 diabetes mellitus.

Gaete. Menstrual cycle in type 1 diabetes. Fertil Steril 2010.

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sented as the mean ± SD. A significance level of 5% was used. All statistical calculations were performed with use of Stata 10.5 (StataCorp, College Station, TX).

RESULTS

The clinical characteristics of both groups, as well as diabetes control in the group with type 1 diabetes mellitus, are shown in Table 1. By design, both groups exhibited similar gynecologic age and BMI. The group with type 1 diabetes mellitus demonstrated delayed menarche and were older by half a year compared with the control girls.

Menstrual cycle characteristics are shown in Table 2. Both groups of girls were followed for a similar period of time. Girls with type 1 diabetes mellitus had a longer menstrual cycle and a higher CV. In addition, girls with type 1 diabetes mellitus had a higher prevalence of oligomenorrhea (odds ratio [OR] = 5.9; confidence interval [CI] = 2.5–13.7) and borderline significance for amenorrhea (OR = 6.6; CI = 0.7–56.8). The presence of type 1 diabetes mellitus was a significant factor associated with the presence of in the former menstrual cycle abnormality, even after adjusting for gynecologic age and BMI-SD score (β = 1.886, SEM: 0.451, Wald = 17.5, $P < .0001$). The proportion of girls having at least one cycle with an abnormal duration was 81% and 59% of the girls with type 1 diabetes mellitus and controls, respectively (OR = 5.9; CI = 2.5–13.7; $P < .05$). The prevalence of polymenorrhea was similar in both groups.

Girls with type 1 diabetes mellitus with different degrees of metabolic control were compared with the control group (Table 3). Patients were classified as having optimal metabolic control if their HbA1c level was 7.59% or lower, intermediate control if their HbA1c was 7.6% to 8.9%, and insufficient metabolic control if their HbA1c was 9% or higher (14). Girls with type 1 diabetes mellitus with optimal metabolic control displayed a similar cycle duration, CV, and age of menarche compared with control girls. However,

TABLE 2

Characteristics of menstrual cycle in girls with type 1 diabetes mellitus compared with the control group.

	Type 1 diabetes mellitus (n = 56)	Control (n = 56)
Duration of follow-up (mo)	5.4 ± 1.4	5.3 ± 2.1
No. of cycles studied	4.2 ± 18.0	4.9 ± 1.5[a]
CV (%)	29.7 ± 19.0	23.7 ± 18.4[a]
SD of the cycles	13.7 ± 14.3	8.0 ± 8[a]
Cycle duration (d)	48.0 ± 38.9	32.0 ± 6.9[b]
All cycles were normal (%)	19.6	41.0[a]
Girl had at least one cycle with		
Oligomenorrhea (%)	58.9	19.6[c]
Amenorrhea (%)	10.7	1.8[d]
Polymenorrhea (%)	39.3	44.6

Note: Data are presented as the mean ± SD.
[a] $P < .05$ compared with type 1 diabetes mellitus.
[b] $P < .01$ compared with type 1 diabetes mellitus.
[c] $P < .001$ compared with type 1 diabetes mellitus.
[d] $P = .05$ compared with type 1 diabetes mellitus.

Gaete. Menstrual cycle in type 1 diabetes. Fertil Steril 2010.

they had a higher prevalence of oligomenorrhea (OR = 4.7; CI = 1.4–15.7). The group of girls with type 1 diabetes mellitus with intermediate metabolic control (HbA1c = 7.6–8.9) exhibited longer cycle duration, higher CV, and a greater prevalence of oligomenorrhea (OR = 10.6; CI = 3.1–36.2) compared with control adolescents. Girls with type 1 diabetes mellitus with an HbA1c >9% displayed a longer cycle duration, delayed menarche, and a higher prevalence of oligomenorrhea (OR = 4.9: CI = 1.7–14.3), higher prevalence of amenorrhea (OR = 12.2; CI = 1.3–116.5), and lower frequency of polymenorrhea (OR = 0.3; CI = 0.1–0.9).

A positive correlation was observed between HbA1c levels and cycle duration (r=0.3, P=.025) and between daily insulin dose and CV (r = 0.3, P=.028). Regression analysis performed for the group with type 1 diabetes mellitus showed that cycle duration was affected by HbA1c levels (P=.025, B = 5.08) but not by gynecologic age and insulin dose, suggesting that for each point that HbA1c increases, the menstrual cycle is prolonged by 5 days. Coefficient of variation in girls with type 1 diabetes mellitus was associated with insulin dose (P=.038, B = 12.5) but not with gynecologic age or HbA1c levels. Age of menarche was not a significant factor in the presence of oligomenorrhea in either group. Logistic regression did not identify any significant factor associated with the presence of oligomenorrhea in girls with type 1 diabetes mellitus.

DISCUSSION

We report a prospective study of menstrual cycle abnormalities in adolescents with type 1 diabetes mellitus. Our results suggest that some abnormalities of the menstrual cycle are observed in girls with optimal metabolic control but that menstrual irregularities become more severe with poor metabolic control. Girls with optimal metabolic control exhibit twice the prevalence of oligomenorrhea compared with control girls, in spite of having normal mean menstrual cycle length and CV. Menstrual abnormalities were prevalent in girls with intermediate metabolic control. This group of adolescents displayed longer and more irregular cycles, and 70% of them reported at least one cycle >45 days.

We observed that 60% of the girls with type 1 diabetes mellitus had at least one episode of oligomenorrhea during the 6-month observation period, significantly higher than the 20% observed in control girls. These results are similar to those previously reported for adolescents by Adcock et al. (15) and for young women by Strotmeyer et al. (1). However, this prevalence is higher than the 20% to 30% reported by several groups for adults with type 1 diabetes mellitus (1–3, 16, 17) and suggests that menstrual irregularities should be included in the list of problems that are critical during adolescence for girls with type 1 diabetes mellitus, but which become less severe afterwards.

Girls with type 1 diabetes mellitus had a mean cycle duration of 48 days, significantly higher than the 32 days observed in the control group and than the 34 days reported in previous reports of healthy adolescents (10, 12, 13). HbA1c level was the only identified risk factor in determining menstrual cycle length in type 1 diabetes mellitus, and regression analysis showed that for each point increase in HbA1c the menstrual cycle duration was prolonged by 5.1 days.

TABLE 3

Characteristics of menstrual cycles according to metabolic control in girls with type 1 diabetes mellitus compared with the control group.

	Type 1 diabetes mellitus; HbA1c (%)			
	<7.6	7.6–8.9	>9	Control
No.	15	18	23	56
Menarche (y)	12.2 ± 0.9	12.5 ± 1.4	13.0 ± 1.3[a]	12.1 ± 1.0
Menstrual cycle duration (d)	34.9 ± 8.9	48.6 ± 34[b]	57 ± 52.3[c]	32.0 ± 6.9
CV (%)	27.6 ± 15.6	35.5 ± 17.8[b]	27.4 ± 21.7	23.7 ± 18.4
Girl had at least one cycle with				
Oligomenorrhea (%)	53.3[b]	72.2[c]	54.5[a]	19.6
Amenorrhea (%)	0	11.1	18.2[b]	1.8
Polymenorrhea (%)	60.0	50.0	18.2[b]	44.6

Note: Data are presented as the mean ± SD.
[a] $P < .01$ compared with the control group.
[b] $P < .05$ compared with the control group.
[c] $P < .001$ compared with the control group.

Gaete. Menstrual cycle in type 1 diabetes. Fertil Steril 2010.

Several mechanisms may explain the detrimental effect of uncontrolled type 1 diabetes mellitus on menstrual cycle length (18). Hypogonadotropic hypogonadism was shown in women with type 1 diabetes mellitus with uncontrolled diabetes (19, 20). These findings subsequently were confirmed in mice knocked out for the brain insulin receptor, which also develop hypogonadotropic hypogonadism (21). Recently, Castellano et al. (22, 23) demonstrated that insulin-deficient mice with streptozocin-induced diabetes have hypogonadism due to decreased kisspeptin expression in the hypothalamus and that administration of kisspeptin restores gonadotropin and steroid levels in these animals.

The importance of the presence of residual β-cell function on the presence of amenorrhea was previously demonstrated by Prelevic et al. (24). These data lead to the hypothesis that the girls in our study with optimal metabolic control and normal menstrual cycle duration and variability may have some degree of residual β-cell function that protects them against menstrual irregularities. A second mechanism explaining the association of hyperglycemia with longer menstrual cycles may be the direct effect of hyperglycemia on the ovaries. Chang et al. (25) showed that hyperglycemia in mice delays oocyte maturation and increases apoptosis.

Our study evaluated the variability of cycle length in determining the CV. The variability in cycle length was higher in adolescents with type 1 diabetes mellitus, especially in those with intermediate metabolic control. Cycle variability increased with higher insulin doses, even when adjusted for HbA1c levels and gynecologic age. We postulate that higher insulin doses may affect ovarian steroidogenesis or folliculogenesis, leading to irregular cycles (26, 27). Insulin and insulin-like growth factor I receptors are present in all compartments of the ovary, including theca, granulosa, and stromal cells (27, 28). In vitro studies of theca cells obtained from healthy women have shown that insulin stimulates steroidogenesis and folliculogenesis (27, 28). These data suggest that irregular menstrual cycles may depend on a direct effect of insulin on the ovary.

This is the first report of an increased variability of the menstrual cycle in girls with type 1 diabetes mellitus. However, we postulate that longer menstrual cycles and the higher prevalence of oligomenorrhea we observed are associated more clearly with reproductive morbidity than with menstrual cycle variability. Oligoanovulation, hyperandrogenism, abnormal menstrual bleeding, and endometrial hyperplasia are associated with longer cycles but not with greater variability of the menstrual cycle (29, 30). The higher incidence of endometrial carcinoma observed in women with type 1 diabetes mellitus could be related to the high prevalence of oligomenorrhea (31).

Several endocrine findings also have been associated with menstrual irregularities in women with type 1 diabetes mellitus. Functional ovarian hyperandrogenism (32–34), decreased sex hormone-binding globulin and insulin-like growth factor I levels (15, 24), an increased LH/FSH ratio (15), and a high prevalence of polycystic ovaries (15) have been described in type 1 diabetes mellitus with menstrual irregularities. These findings suggest that menstrual irregularities in type 1 diabetes mellitus may indicate some degree of ovarian hyperandrogenism, and other deleterious endocrine profiles may be present in these girls (33).

The strength of this article is the prospective follow-up of the menstrual cycles. Several measures were undertaken to be sure that there was a proper register of the menses; however, there is no way to be completely sure of the reliability of menstrual cycle history in adolescents. The limitations of this study include the lack of measurement of hormone levels that could explain the menstrual irregularities.

Other possible reasons for menstrual irregularities may be the presence of high titers of ovarian autoantibodies in girls with type 1 diabetes mellitus (35). Snajderova et al. (35) studied 53 girls with type 1 diabetes mellitus and observed that ovarian autoantibodies were present in 70% of these girls and in only 5% of the control girls.

Similar to previous reports (36–38), menarche was delayed in type 1 diabetes mellitus, especially in those girls with higher HbA1c. Delayed menarche in women without diabetes is associated with a higher risk of menstrual irregularities (39). The group of girls with unsatisfactory metabolic control exhibited a higher prevalence of amenorrhea, delayed menarche, and several of the factors known to decrease bone mass in women with type 1 diabetes mellitus (40).

In conclusion, adolescents with type 1 diabetes mellitus exhibited longer menstrual cycle duration and greater variability in cycle duration, as well as higher rates of oligomenorrhea, which are dependent on HbA1c levels and insulin dose. Girls with optimal metabolic control exhibited a higher prevalence of oligomenorrhea, but the mean cycle duration and variability was normal. We conclude that menstrual irregularities are a prevalent problem during adolescence despite multiple daily insulin doses. All efforts should be aimed at improving metabolic control in patients with type 1 diabetes mellitus, but future studies should evaluate the physiopathology and treatment of oligomenorrhea in patients with type 1 diabetes with optimal metabolic control (1).

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