Menstrual Cycle Differences Between Women With Type 1 Diabetes and Women Without Diabetes

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OBJECTIVE — To evaluate menstrual cycle histories among women with type 1 diabetes, their sisters, and unrelated control subjects without diabetes across all reproductive ages.

RESEARCH DESIGN AND METHODS — Menstrual and reproductive histories were obtained by questionnaire from 143 women with type 1 diabetes, 186 sisters without diabetes, and 158 unrelated control subjects without diabetes participating in the Familial Autoimmune and Diabetes study.

RESULTS — Women with type 1 diabetes had more menstrual problems (long cycles, long menstruation, and heavy menstruation) before age 30 years than sisters and control subjects. These differences were all statistically significant, except for heavy menstruation at age <20 years. No differences were observed after age 30 years. Women with type 1 diabetes experienced later menarche, earlier natural menopause, fewer pregnancies, and more stillbirths than women without diabetes. Multiple regression analyses revealed that type 1 diabetes caused an approximate twofold increased risk of any menstrual problem before age 30 years. These were primarily related to long cycles and long menstruation in women aged <20 and 20–29 years, as well as with heavy menstruation from 20 to 29 years. Oral contraceptives were protective for any menstrual problem and heavy menstruation from 30 to 39 years of age. With history of pregnancy from 20 to 40 years of age, any menstrual problem and long menstruation were more likely.

CONCLUSIONS — The results suggest that type 1 diabetes is an independent risk factor for menstrual disturbances in young adults. Future studies may determine whether addressing menstrual disturbances improves quality of life and health for these women.

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Women with type 1 diabetes are likely to report menstrual disorders, including a later age at menarche (1–4). Type 1 diabetes is thought to disrupt normal hypothalamic-pituitary–gonadal function, particularly if the disease is poorly controlled (5,6), and thereby affects menstrual cycles and other reproductive outcomes (3,7,8). However, little is known about the natural history of menstruation among women with type 1 diabetes compared with women without diabetes across all ages in the reproductive lifespan. Few studies on menstrual disorders and type 1 diabetes have included comparison groups without diabetes. Furthermore, the role of possible familial factors in menstrual characteristics of women with type 1 diabetes is unclear. In case-control studies of menstrual cycles, women with type 1 diabetes report a significantly greater prevalence of dysfunction and irregularity of menstruation (3,4,8), such as oligomenorrhea and amenorrhea (1,3,8,9). Other menstrual cycle characteristics, such as duration or heaviness of menstruation, have not been well studied for type 1 diabetes. Additionally, researching menstrual variability may ultimately identify women at high risk for diseases of aging such as osteoporosis and cardiovascular disease (10), which are known complications of type 1 diabetes.

This study was conducted to determine whether women with type 1 diabetes have a greater prevalence of menstrual irregularities (including cycle length, menstruation length, and heavy menstruation) across the reproductive lifespan. To address this question, we evaluated menstrual cycles of women with type 1 diabetes from the Pittsburgh registry and compared them with their sisters and unrelated control subjects without diabetes. These menstrual characteristics may impact quality of life and reproductive health for women with type 1 diabetes. Menstrual cycle disturbances may be inadequately addressed as a complication of type 1 diabetes.

RESEARCH DESIGN AND METHODS

Study population

The women were participants in the Familial Autoimmune and Diabetes (FAD) study. The FAD study was based on the Children's Hospital of Pittsburgh type 1 Diabetes Registry for 1950–1965 and was previously described in detail (11). In addition to type 1 diabetes cases (n = 265 of 375), living parents and siblings of these probands were invited to participate in the FAD study, of which 73.6% enrolled in the study (n = 635 of 868). As previ-

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Abbreviations: FAD, Familial Autoimmune and Diabetes.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Descriptive characteristics of women with and without type 1 diabetes*

		Without diabetes		
	Type 1 diabetes	Sisters	Control subjects	*P*
n	143	186	158	
Mean age at exam (years)	42.6 ± 5.4	42.4 ± 8.3	41.2 ± 6.4	0.22
Age at menarche (years)	13.5 ± 1.9	12.5 ± 1.4	12.6 ± 1.4	<0.001
Ever oral contraceptive use (%)	44.0	79.0	79.8	<0.001
Ever pregnant (%)	76.8	83.9	70.3	0.01
Mean number of pregnancies*	2.3 ± 1.6	2.9 ± 1.4	2.6 ± 1.4	<0.001
Infertility (%)	16.9	17.7	16.6	0.96
Miscarriages (%)*	31.2	32.1	27.9	0.76
Stillbirths (%)*	10.1	0.6	0.9	<0.001
Natural menopause (%)	12.5	12.7	9.8	0.69
Mean age at natural menopause (years)†	41.6 ± 10.6	49.9 ± 6.1	47.8 ± 4.6	0.06
Ever smoked (%)	41.8	48.4	50.0	0.33
College attendance (%)	64.6	65.6	75.9	0.06
Income ≥$40,000 (%)	40.8	59.1	52.7	0.006
Mean BMI (kg/m^2)	24.6 ± 4.5	25.2 ± 5.3	27.4 ± 7.3	0.003
Hashimoto's thyroiditis (%)	42.7	30.4	19.6	<0.001
Age Hashimoto's detected (years)	38.1 ± 9.3	42.0 ± 10.2	39.2 ± 9.7	0.14

Data are mean ± SD. *These analyses excluded women that had never been pregnant; †these analyses excluded women with a premenopausal hysterectomy or bilateral oophorectomy and were based on 120, 165, and 143 women, respectively, of whom 15, 21, and 14 experienced natural menopause.

ously detailed (11), 96 control families without diabetes were enrolled, representing >90% of families in Allegheny County that responded to recruitment and were eligible to participate.

Methods and data collection

FAD study participants had clinical evaluations at the Diabetes Research Center in Pittsburgh, through out-of-town examinations, or during home visits. Examinations included an assessment of autoimmune diseases, blood pressure, and BMI. A blood sample was obtained to measure lipid levels, HbA_{1c}, autoantibodies, and thyroid function. The diagnosis of thyroid disease was based on clinical evaluation, medical history, assessment of signs and symptoms, and laboratory determinations, as previously described (12). Few women had Graves' disease; thus, only Hashimoto's thyroiditis was addressed in analyses.

Gynecological information, including menstrual histories, pregnancies and their outcome, and hormone use, was obtained by survey for all women. The survey instrument was adapted from the Healthy Women Study, which was designed to follow women through the menopausal transition (13,14). Age at menarche, menstrual regularity, menstrual duration and heaviness, and menstrual cycle length were self-reported for each of the following age ranges: <20, 20–29, 30–39, 40–49, and ≥50 years. Data on oral contraceptive and hormone replacement therapy use were also collected for these age ranges. Further questionnaire data included current and past medical history (e.g., macro- and microvascular complications) and lifestyle factors (e.g., smoking, physical activity, nutrition, education, and socioeconomic status).

Statistical analyses

χ^2 tests were performed to evaluate differences in prevalence and univariate associations across groups. Exact methods were used when the expected value of any cell was <5. For continuous variables, nonparametric one-way Mann-Whitney U tests and Kruskal-Wallis *H* tests were performed for univariate comparisons between two groups and among three groups, respectively. All univariate analyses were conducted with SPSS software (SPSS, Chicago). Multivariate analyses were completed using stepwise multiple logistic regression with the SAS system (SAS, Cary, NC).

RESULTS

Description of participants

For the women with type 1 diabetes, their sisters, and control subjects, mean age at clinic exam was ~42 years. The mean age of diabetes onset was 8.1 ± 5.1 years. Microvascular complications were present in 70% of women with diabetes, and macrovascular complications were present in 29%. As shown in Table 1, sisters and unrelated control subjects without diabetes had a similar age at menarche, prevalence of infertility, and mean number of pregnancies; other sociodemographic characteristics, such as oral contraceptive use, smoking, and income level, were also similar. Women with type 1 diabetes experienced menarche nearly a year later than sisters and control subjects (13.5 vs. 12.5 vs. 12.6 years, $P < 0.001$), and age at self-reported natural menopause, defined as >12 months without menstruating, was almost 10 years earlier (41.6 vs. 49.9 vs. 47.8 years, $P = 0.06$). No difference in age of menarche existed for cases with age of diabetes onset <10 vs. ≥10 years (13.7 vs. 13.1 years, $P = 0.16$), and no correlation existed between age of menarche and age of onset ($r = 0.04$, $P = 0.60$). However, cases with age of onset <10 years had menarche significantly later than women without diabetes ($P < 0.001$), whereas those with age of onset ≥10 years did not ($P = 0.07$). Of those with history of pregnancy, women with diabetes had fewer pregnancies compared with sisters and control subjects (2.4 vs. 2.9 vs. 2.6, $P < 0.001$). Oral contraceptive use

Table 2—*Self-reported menstrual cycle characteristics of women with and without type 1 diabetes by age range*

		Without diabetes		
	Type 1 diabetes	Sisters	Control subjects	*P*
<20 years of age (*n*)	143	186	158	
Bleeding ≥6 days	56.5	41.6	47.7	0.04
Cycles >31 days	24.8	14.3	17.8	0.07
Heavy bleeding	25.2	18.1	22.4	0.31
Any irregularity	78.7	64.3	66.7	0.02
20–29 years of age (*n*)	143	186	158	
Bleeding ≥6 days	52.8	38.7	40.5	0.04
Cycles >31 days	22.1	8.0	12.3	0.002
Heavy bleeding	27.0	14.7	21.0	0.03
Any irregularity	76.8	55.4	55.5	<0.001
30–39 years of age (*n*)	141	180	152	
Bleeding ≥6 days	44.8	41.1	36.2	0.36
Cycles >31 days	11.9	8.4	8.3	0.53
Heavy bleeding	25.0	18.6	25.2	0.29
Any irregularity	67.5	57.9	53.8	0.08
40–49 years of age (*n*)	100	114	91	
Bleeding ≥6 days	40.8	36.0	29.0	0.34
Cycles >31 days	8.6	11.1	10.4	0.87
Heavy bleeding	21.6	27.5	29.2	0.55
Any irregularity	67.6	67.4	62.1	0.74

Data are %.

was significantly less common in women with diabetes than sisters and control subjects (44.0 vs. 79.0 vs. 79.8%, $P < 0.001$). Although women with type 1 diabetes, sisters, and control subjects reported similar rates of infertility, defined as attempting to become pregnant for >1 year without success and miscarriages, the proportion of pregnant women experiencing stillbirths was significantly higher for those with diabetes (10.1 vs. 0.6 vs. 0.9%, $P < 0.001$).

BMI at clinic visit and lifestyle variables, including smoking, yearly household income, and education, were compared for women with and without diabetes. Mean BMI at clinic visit was significantly lower among women with type 1 diabetes than sisters and control subjects (24.6 vs. 25.2 vs. 27.4 kg/m^2, $P = 0.003$). No differences in smoking (ever/never) existed among cases compared with sisters and control subjects (41.8 vs. 48.4 vs. 50.0%, NS). The percentage attending college was slightly lower among cases and sisters (64.6 vs. 65.6 vs. 75.9%, $P = 0.06$). The proportion with yearly household income ≥$40,000 was significantly lower among women with type 1 diabetes compared with sisters and control subjects (40.8 vs. 59.1 vs. 52.7%, $P < 0.006$).

Rates of Hashimoto's thyroiditis were significantly different for women with type 1 diabetes, their sisters, and control subjects (test of trend: $P < 0.001$). The highest prevalence was found for women with type 1 diabetes (42.7%), and sisters had a somewhat higher prevalence (30.4%) compared with control subjects (19.6%). Each group had a similar mean age of detection of Hashimoto's thyroiditis. Age of diagnosis was self-reported if previously diagnosed, or age at clinic visit was used if cases were newly diagnosed. The prevalence of hypothyroid Hashimoto's disease was significantly different for cases, sisters, and control subjects (20 vs. 15 vs. 10%), as was euthyroid Hashimoto's disease (23 vs. 15 vs. 10%) ($P = 0.001$).

Univariate comparisons of menstrual characteristics

Self-reported menstruation ≥6 days, menstrual cycles >31 days, and heavy menstruation were considered to be menstrual problems. Women with and without diabetes experiencing these problems are described in Table 2 for age ranges <20, 20–29, 30–39, and 40–49 years. Women with diabetes more frequently reported all of these menstrual problems for age ranges <20 and 20–29 years. In particular, self-report of any menstrual problem, defined as menstrual irregularity, menstruation lasting ≥6 days, cycles >31 days, or a heavy menstruation, was higher among women with diabetes than sisters and control subjects for age ranges <20 years (78.7 vs. 64.3 vs. 66.7%, $P = 0.02$) and 20–29 years (76.8 vs. 55.4 vs. 55.5%, $P < 0.001$). From 30 to 39 and 40 to 49 years of age, differences by diabetes status were not statistically significant.

Since Hashimoto's thyroiditis may influence menstrual patterns and >40% of type 1 diabetes cases were affected, stratified analyses were performed. Analyses were restricted to the older age-groups because few cases of Hashimoto's thyroiditis were detected before age 30 years ($n = 8$). Type 1 diabetes cases with Hashimoto's thyroiditis from 30 to 39 ($n = 31$) and 40 to 49 years of age ($n = 55$) had no significant differences in any menstrual problem compared with cases without the disease ($n = 109$ and $n = 85$, respectively): menstruation ≥6 days (30–39 years: 38 vs. 46%, $P = 0.45$; 40–49 years: 28 vs. 35%, $P = 0.42$), cycles >31 days (30–39 years: 17 vs. 11%, $P = 0.47$; 40–49 years: 5 vs. 11%, $P = 0.52$), heavy menstruation (30–39 years: 22 vs. 25%, $P = 0.73$; 40–49 years: 17 vs. 32%, $P = 0.09$), or any menstrual problem (30–39 years: 68 vs. 67%, $P = 0.89$; 40–49 years: 61 vs. 66%, $P = 0.60$). When age of diagnosis was not considered and women were classified as hypothyroid, euthyroid, or having no Hashimoto's disease, euthyroid cases had heavier bleeding in their twenties than cases with hypothyroidism or no Hashimoto's disease (45.8 vs. 34.6 vs. 18.4%, $P = 0.02$).

To assess possible additional confounding factors, stratified analyses were also performed for oral contraceptive use, BMI at clinic visit, diabetes complications (micro- and macrovascular) and HbA_{1c} values. No differences in menstrual characteristics existed among women with type 1 diabetes using oral contraceptives compared with nonusers for any age range. No relationship with high BMI (≥25 kg/m^2), microvascular complications, macrovascular complications, or high HbA_{1c} (>8%) at clinic visit and menstrual characteristics existed among

Table 3—*Final multivariate logistic regression models*, by age range: ORs, 95% CIs, and P values for risk factors for self-reported menstrual cycle irregularities*

Age range	Cycle length >31 days	*P*	Menstrual bleeding ≥6 days	*P*	Heavy menstrual bleeding	*P*	Any menstrual problems	*P*
<20 years								
Type 1 diabetes	1.7 (1.0–2.9)	0.03	1.6 (1.1–2.5)	0.02	1.3 (0.83–2.2)	0.24	2.0 (1.2–3.2)	0.006
20–29 years								
Type 1 diabetes	2.6 (1.5–4.5)	0.001	1.7 (1.1–2.6)	0.01	1.7 (1.1–2.8)	0.03	2.5 (1.6–4.1)	<0.001
Ever pregnant	—		2.0 (1.3–3.0)	0.001	—		1.7 (1.1–2.5)	0.02
30–39 years								
Type 1 diabetes	1.5 (0.75–2.9)	0.26	1.3 (0.84–2.0)	0.23	1.1 (0.65–1.8)	0.77	1.5 (0.92–2.3)	0.11
Ever pregnant	—		1.7 (1.0–2.7)	0.03	—		1.9 (1.3–3.0)	0.01
Oral contraceptive use	—		—		0.45 (0.24–0.85)	0.01	0.60 (0.37–0.99)	0.04
40–49 years								
Type 1 diabetes	0.78 (0.29–2.1)	0.62	1.5 (0.86–2.8)	0.15	0.71 (0.37–1.4)	0.30	1.1 (0.63–2.1)	0.65

*Type 1 diabetes was included in all final models. Variables not reported in Table 3 were nonsignificant and therefore excluded from the final model. Age at menarche and Hashimoto's status (hypothyroid, euthyroid, or non-Hashimoto's thyroiditis) at clinic visit were not significant in any model.

women with type 1 diabetes for any age range.

Multiple logistic regression

Three separate models (long cycle length, long menstruation, and heavy menstruation) were performed for each age range (<20, 20–29, 30–39, and 40–49 years). Type 1 diabetes status, age of menarche, oral contraceptive use, ever/never pregnant, and ever/never Hashimoto's thyroiditis (no Hashimoto's, euthyroid, or hypothyroid disease) were entered in each stepwise multiple logistic regression model for women with diabetes, sisters, and control subjects, because these variables showed significant variation among the three groups in univariate analyses. Oral contraceptive use and ever/never pregnant were age-range specific. For ages <20 and 20–29 years, type 1 diabetes was associated with cycle length >31 days (odds ratio [OR] 1.7, 95% CI 1.0–2.9 and 2.6, 1.5–4.5, respectively) and menstruation ≥6 days (1.6, 1.1–2.5 and 1.7, 1.1–2.6) (Table 3). Type 1 diabetes status was also associated with heavy menstruation for age range 20–29 years (2.5, 1.6–4.1).

Variables in addition to diabetes influenced the various menstrual problems. Oral contraceptive use was protective for heavy menstruation in women aged 30–39 years (OR 0.45, 95% CI 0.24–0.85). History of pregnancy was also associated with longer menstruation in women aged 20–29 (2.0, 1.3–3.0) and 30–39 years (1.7, 1.0–2.7). Menstrual cycle problems were not significantly affected by age of menarche or Hashimoto's thyroiditis.

The same variables described above were entered in a stepwise multiple logistic regression model for report of any menstrual problem in age ranges <20, 20–29, 30–39, and 40–49 years. Type 1 diabetes was independently associated with any menstrual problem in age ranges <20 (OR 2.0, 95% CI 1.2–3.2) and 20–29 years (2.5, 1.6–4.1), although not in older age ranges. Women with a history of pregnancy were more likely to have a menstrual problem from 20 to 29 (1.7, 1.1–2.5) and 30 to 39 years of age (1.9, 1.3–3.0). In the age range 30–39 years, oral contraceptive use was protective against any menstrual problem (0.60, 0.37–0.99).

CONCLUSIONS — The natural history of many menstrual characteristics across all ages, particularly in the 30s and 40s, has never been reported before in women with type 1 diabetes. Although menstrual irregularities in type 1 diabetes were described nearly 50 years ago (1), few epidemiologic studies were performed. Only cycle length irregularities were previously reported in those aged 18–49 years (median 32) (3), adolescents (8), and young women (mean age 22 years) (9). Cawood et al. (4) examined cycle length, period length, and heaviness in younger women (mean age 31 years) but not by age range or in a population-based sample. Our population was older than previous studies, providing more information on later reproductive years. Unlike the current study, none of these studies compared women with their nondiabetic sisters in order to attempt to adjust for possible familial similarities of menstruation.

In multivariate models that adjusted for confounding factors, type 1 diabetes was independently associated with long cycle length, long menstruation, heavy menstruation, and report of any menstrual problem only at younger age ranges. However, these trends were not significant for older age ranges, as the women move closer to the end of their reproductive years. While experiencing menstrual problems in the earlier reproductive years may not be unusual (10), it may be even more likely for women with diabetes, and moreover, it appears to persist throughout their 20s.

Several authors have also reported an ~1-year delay in menarche with type 1 diabetes as well as a later menarche among those with an earlier age at onset (1–4,9). In contrast to the findings of Schriock et al. (15) for nonregistry cases, we noted that only cases with age of onset <10 years had a later menarche. Diabetes onset before puberty may disrupt the hypothalamic-pituitary-gonadal axis and/or cause weight loss, decreasing body fat important for menarche to occur (6,7,16).

The decrease in pregnancies, high number of miscarriages, and increase in stillbirths for our population of women with diabetes was previously reported (17). Other studies also found that while women with and without diabetes were equally parous, those with diabetes had

fewer children (4,18). Since this cohort was a younger reproductive age at previous report (17), the higher number of stillbirths may be due to advanced maternal age (19). Miscarriage prevalence, dependent on methods for ascertaining pregnancy and loss, was similar for women with and without diabetes but higher than some reports for nondiabetic women (20,21), possibly due to higher prevalence of other autoimmune diseases in the sisters, particularly Hashimoto's thyroiditis (11,22,23). However, Wilcox et al. (24) recently showed prospectively that 25% of pregnancies in healthy women end in miscarriage. If our nondiabetic women were not reproductively healthy, it would have lessened our ability to detect menstrual cycle differences.

The earlier self-reported natural menopause in women with type 1 diabetes was previously published (11), and we are currently conducting a prospective study to validate this finding using hormonal measures and menstrual cycle records. If women with type 1 diabetes are also having an earlier menopause, this may be caused by similar underlying etiology that predisposes them to menstrual irregularities. Since the mean age of self-reported natural menopause in the women with type 1 diabetes was 42 years, retrospective analyses of menstrual characteristics for their thirties and forties may actually be describing perimenopausal symptoms. Two possible causes for menstrual cycle dysfunction in these women may be decreased hypothalamic drive or decreased count/quality of oocytes due to an increased rate of atresia, possibly through effects of insulin (6). The hypothalamic gonadotrophin-releasing hormone pulse generator slows, decreasing luteinizing and follicle-stimulating hormone stimulation (6). In particular, this may occur in women with poor diabetes control (5–7). We did not find any differences in menstrual problems related to metabolic control when stratifying by HbA_{1c} at clinic visit, although this may not reflect control over long periods or earlier in the lifetime.

Hashimoto's thyroiditis was not associated with menstrual disturbances in multivariate analyses. The literature suggests an association of menstrual problems, such as menorrhagia (excessive blood loss) and increased cycle length with hypothyroidism (25–27), and from 20 to 29 years of age, we showed that cases with Hashimoto's thyroiditis at clinic exam had significantly heavier menstruation. One reason further associations were not found may be that most menstrual problems occurred before Hashimoto's thyroiditis diagnosis, or hypothyroidism. Women also may have been adequately treated for their thyroid disease and less likely to exhibit menstrual problems (27).

As with any retrospective study utilizing self-report data, a potential for recall bias exists. However, self-report reproductive data for this population of women with type 1 diabetes was shown to be valid and reliable (17). Ideally, these menstrual characteristics should be collected prospectively along with data on diabetes control and hormone levels. While we obtained age-specific menstrual characteristics, oral contraceptive use, and births, age-specific BMI measures were not available, although stratified analyses for BMI at clinic visit showed no differences in menstrual problems.

In summary, women with type 1 diabetes are more likely to experience menstrual problems throughout their primary reproductive years, as compared with their sisters and unrelated female control subjects. A prospective study of menstruating women with type 1 diabetes is needed to validate these findings and assess the impact of these problems.

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