Ovulation rate in adolescents with type 1 diabetes mellitus

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Objective: To study ovulation in adolescents with type 1 diabetes (T1D) and the effect of hemoglobin A1c (HbA1c) levels on their ovulatory function.
Design: Prospective investigation.
Setting: Academic research institute.
Patient(s): Adolescents with T1D (n = 31) and healthy girls (n = 52).
Intervention(s): Ovulation assessed through the measurement of salivary progesterone (days 13, 18, 23, and 28 of each cycle).
Main Outcome Measure(s): Proportion of ovulatory cycles.
Result(s): A total of 168 and 281 menstrual cycles were studied in the T1D and control girls, respectively. Metabolic control was defined as optimal if HbA1c was <7.5%. The proportion of ovulatory cycles was similar in the TID and control groups (34.5% and 36.3%, respectively). Regression analyses showed that the presence of T1D did not have a statistically significant effect on the ovulatory rate. However, more ovulatory cycles were observed in girls with T1D who had optimal metabolic control compared with those who had insufficient control (51.3% vs. 29.4%).
Conclusion(s): In adolescent girls, T1D did not affect the rate of ovulation. A higher ovulatory rate was observed in those with optimal control compared with those with insufficient metabolic control, but a substantial proportion of ovulatory cycles were still observed in patients with higher HbA1c levels. (Fertil Steril® 2011;95:197–202. ©2011 by American Society for Reproductive Medicine.)

Key Words: Adolescence, fertility, menarche, ovarian function, ovulation, pregnancy, puberty, type 1 diabetes mellitus

Several abnormalities in ovarian function have been described in adolescents and adult women with type 1 diabetes (T1D), but there have been no studies evaluating ovulatory function in these patients (1). A decreased duration of the reproductive span in women with T1D due to delayed menarche (1–3), earlier menopause (4), and earlier decline of ovarian reserve (5) has been described. In addition, the presence of ovarian hyperandrogenism (6, 7), menstrual cycle abnormalities (8), and some degree of hypogonadism in women with poor metabolic control (1) may decrease fertility in these patients. However, the question of whether ovulatory function is affected during puberty in girls with T1D remains unanswered.

The study of ovulatory function is relevant for young adolescents with T1D who may not be fully aware of their risk of pregnancy. Women with T1D should have formal preconception care to prepare them for pregnancy; as recently recommended by the ADA and the Australasian Diabetes in Pregnancy Society, an hemoglobin A1c (HbA1c) level lower than 7% or close to 6% should be achieved before becoming pregnant (9, 10). Despite this recommendation, adolescents with T1D, who frequently have unsatisfactory metabolic control during puberty, exhibit behaviors associated with a high risk of unplanned pregnancy and have limited knowledge about pregnancy and diabetes (11, 12).

The prevalence of abnormalities in ovarian function may be associated with insufficient metabolic control (1). We prospectively studied a group of adolescent girls with T1D who were treated with multiple insulin doses, and we observed a higher rate of oligomenorrhea, amenorrhea, and menstrual cycle variability in comparison with nondiabetic adolescent girls (8). The girls with T1D had menstrual cycles of increased duration, which was associated with poor metabolic control. More specifically, for each percentage point of increase in HbA1c level, there was a 5-day increase in the duration

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of the menstrual cycle. Therefore, we hypothesized that the ovulatory rate in young adolescent girls with T1D may be decreased, and that the rate of ovulation may be dependent on HbA1c levels and gynecologic age.

MATERIALS AND METHODS

Patients

Young adolescents with T1D and healthy control girls without clinical or biochemical hyperandrogenism were studied. Time after menarche (gynecologic age) is a critical determinant of ovulatory rate for healthy girls, so the girls were recruited if they were close to reaching a determined gynecologic age (13). The younger group of girls who were recruited close to menarche (up to 6 months after menarche) were studied during the ensuing months (first postmenarche year), whereas the second group of girls was recruited close to the second postmenarche year (gynecologic age: 18–29 months) and was studied during the third postmenarche year. The older group of girls was recruited close to the third postmenarche year (gynecologic age: 36–44 months) and were studied during the fourth postmenarche year. Five girls with T1D and 17 control girls were studied during two periods (third postmenarche year and fourth postmenarche year).

Inclusion criteria for girls with T1D were severe insulinopenic diabetes treated with insulin from the time of diagnosis as well as diabetes' duration longer than 2 years. All patients were treated with at least three daily insulin doses of human or analog insulin. The exclusion criteria were the following: clinical or biochemical hyperandrogenism; type 2 or other type of diabetes; honeymoon period defined as an insulin daily requirement lower than 0.5 IU/kg/day and HbA1c lower than 7% (14); abnormal thyroid function; elevated creatinine level; use of contraceptive pills, steroids, or any other type of medication; and the presence of other chronic conditions.

Healthy girls attending schools located near the participating hospitals were invited to participate as controls in the study, and were matched with patients by gynecologic age and body mass index (BMI). Girls without clinical signs of hyperandrogenism or chronic diseases who were not taking contraceptive pills, steroids, or any other type of medication and who had had a normal birth weight and normal age of menarche were included in the study.

The lack of previous reports of ovulatory rate in T1D prompted us to calculate the sample size for this study based on studies of ovulation in adolescents with precocious pubarche (15). Based upon a previously reported proportion of ovulation in 47% and 12% of menstrual cycles in control adolescents and girls with precocious pubarche, a sample size of 40 cycles by group would be required for a power of 90% and α error <0.5. 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.

Ovulation Rate Assessment

The study of ovulation was based on measurements of salivary progesterone (16), as previously described elsewhere (17). Briefly, a fasting salivary sample for measurement of progesterone was obtained after a mouth rinse with clear water on days 13, 18, 23, and 28 of each menstrual cycle. An ovulatory cycle was diagnosed if at least one of the samples had levels of salivary progesterone ≥ 0.06 ng/mL; this criteria had a diagnostic sensitivity and specificity of 80% and 100%, respectively. This threshold level is similar to that reported by Gandara et al. (16). The salivary and serum progesterone levels had a high correlation (Pearson's $r = 0.7178$; 95% CI, 0.4504–0.8671; $P<.0001$), so the maximum salivary progesterone level observed in ovulatory cycles was determined as a measure of luteal function.

Hormone Profile Evaluation

An early morning sample of blood was obtained from both groups of girls during the follicular phase (days 1 to 7) for the measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, 17-hydroxyprogesterone (17OHP), dehydroepiandrosterone sulfate (DHEAS), androstenedione, total testosterone, and sex-hormone–binding globulin (SHBG).

Definitions

Oligomenorrhea was diagnosed if at least one menstrual cycle was longer than 45 days, as was recently suggested by the American Academy of Pediatrics for adolescents (18). The proportion of ovulatory cycles was defined as the fraction of studied cycles that were ovulatory, and was calculated as the number of ovulatory cycles divided by the number of cycles studied in T1D patients or controls, multiplied by 100. Because young girls frequently have anovulatory cycles (18, 19), we decided to report the rate of ovulation as the number of ovulatory cycles per 100 days of follow-up for each girl, which corresponds to the average duration of three menstrual cycles during this period of life (8).

Metabolic control in T1D was classified according to the International Society of Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines as optimal if the HbA1c level was $<7.5\%$ or as insufficient if it was $\geq 7.5\%$ (20).

Laboratory Measurements

The salivary progesterone level was determined by use of a commercial competitive radioimmunoassay kit from Diagnostic System Laboratories (Webster, TX), as previously described elsewhere (17). The assay had a sensitivity of 0.01 ng/mL and an intra-assay and interassay coefficient of variation of 4.8% and 7.2%, respectively. Hormone levels were measured as previously described elsewhere (21). The HbA1c levels were measured using a commercially available automatic system (DCA 2000; Bayer Diagnostics, Tarrytown, NY).

Statistical Analysis

Clinical and laboratory data are shown as mean and standard deviation (SD). The differences in proportions at the different times were evaluated by use of Fisher's exact test. A normal distribution of the variables was assessed by use of the Shapiro-Wilk normality test. Continuous variables were compared with Student's t test or the Mann-Whitney U test for parametric and nonparametric variables, respectively.

The proportion of ovulatory cycles in the girls with T1D according to the degree of metabolic control was evaluated with Pearson's chi-square test. Logistic regression analysis was used to evaluate the effect of diabetes, gynecologic age, and BMI on the proportion of ovulatory cycles. In the T1D group, the effect of optimal metabolic control on the proportion of ovulatory cycles was also assessed by logistic regression after adjustment for gynecologic age and length of the follow-up period.

The correlation of the ovulatory rate with HbA1c levels was assessed using the nonparametric Spearman's rank test. Linear regression analysis was performed to determine the influence of diabetes, gynecologic age, and BMI, adjusted by the length of the follow-up period, on the rate of ovulation (continuous variable). The correlation of the ovulatory rate with HbA1c levels was assessed using the nonparametric Spearman's rank test. Because some girls participated in several periods of the study, we used a mixed generalized equation estimation methodology with an exchangeable covariance matrix to model ovulatory rate for the presence of diabetes, the identification of each girl, and the gynecologic age over ovulatory rate.

All statistical calculations were run on Stata 10.5 (Stata Corporation, College Station, TX) and GraphPad Prism, version 5.0, for Windows (Graph-Pad Software, San Diego, CA). A statistical significance level of 5% was employed.

RESULTS

Clinical and anthropometric characteristics, the duration of the follow-up period, the number of cycles studied of the T1D ($N = 31$) and control ($N = 52$) girls, and the degree of metabolic control and number of daily insulin injections in the patients with T1D are shown in Table 1. A total of 168 and 281 cycles were studied in the T1D and control girls, respectively, which averaged 5.0 and 5.4 cycles per girl, respectively. Menarche was delayed by 1 year in the girls with T1D. Gynecologic age was similar in both groups; however, due to the older age of menarche in T1D as compared with the control girls, the chronologic age was older in the former group. The BMI and height were similar in both groups. The menstrual cycle duration did not differ between the groups. No episode of ketoacidosis was observed

TABLE 1

Clinical characteristics, duration of follow-up period, and menstrual cycle characteristics in controls and in adolescent girls with type 1 diabetes mellitus (T1D), including the duration of diabetes and HbA1c levels in the T1D patients.

	Whole group		Postmenarche year					
			First		Third		Fourth	
	T1D	Control	T1D	Control	T1D	Control	T1D	Control
N	31	52	9	11	13	22	9	19
Age (y)	14.7 ± 1.3	13.9 ± 1.4[a]	13.6 ± 1.5	12.3 ± 1.3	14.6 ± 0.9	13.8 ± 0.8	15.8 ± 1.3	15.0 ± 0.8[a]
BMI (kg/m^2)	22.0 ± 2.3	22.9 ± 3.3	20.9 ± 1.9	21.4 ± 2.1	22.5 ± 2.0	23.1 ± 3.6	22.2 ± 2.8	23.5 ± 3.4
Height (cm)	158.4 ± 4.7	157.6 ± 5.7	156.7 ± 4.8	157.3 ± 5.5	159.9 ± 4.8	157.7 ± 5.8	158.7 ± 4.3	157.6 ± 5.7
HbA1c (%)	8.7 ± 1.4	—	8.9 ± 0.8	—	8.2 ± 1.1	—	9.3 ± 2.1	—
T1D duration (y)	6.7 ± 3.5	—	7.6 ± 3.3	—	7.2 ± 3.6	—	7.5 ± 3.6	—
Menarche (y)	12.7 ± 1.1	11.7 ± 0.9[b]	13.3 ± 1.4	12.0 ± 1.2	12.3 ± 0.9	11.5 ± 0.8	12.5 ± 0.9	11.7 ± 0.7[a]
Gynecologic age (mo)	22.6 ± 13.3	24.8 ± 12.5	4.0 ± 1.9	3.6 ± 1.9	25.4 ± 3.1	24.9 ± 2.6	37.1 ± 3.3	36.9 ± 2.4
Time of follow-up (d)	181.2 ± 71.9	186.8 ± 93.7	205.4 ± 68.0	309.7 ± 96.0[a]	170.5 ± 65.5	145.1 ± 52.7	172.3 ± 85.9	163.8 ± 67.9
Cycles studied per subject (N)	5.4 ± 2.3	5.4 ± 2.3	5.4 ± 2.1	7.5 ± 2.7	5.3 ± 2.1	4.5 ± 1.5	5.6 ± 2.9	5.2 ± 2.2
Cycles studied in the group (N)	168	281	49	83	70	100	49	98
Menstrual cycle (d)	34.7 ± 9.3	35.1 ± 13.0	39.1 ± 10.5	45.4 ± 24.8	32.1 ± 3.2	32.6 ± 5.1	34.1 ± 13.0	32.2 ± 4.7
Oligomenorrhea in ≥1 cycle (%)	11 (35.5)	13 (25.0%)	6 (66.6)	6 (54.4)	4 (30.8)	5 (22.7)	1 (11.1)	2 (10.5)2
Cycles with oligomenorrhea (%)	17 (10.1)	23 (8.2)	12 (25.5)	15 (18.1)	4 (5.7)	6 (6)	2 (2.0)	1 (2.0)

Note: Data are shown as mean ± standard deviation. BMI = body mass index; T1D = type 1 diabetes; HbA1c = hemoglobin A1c.

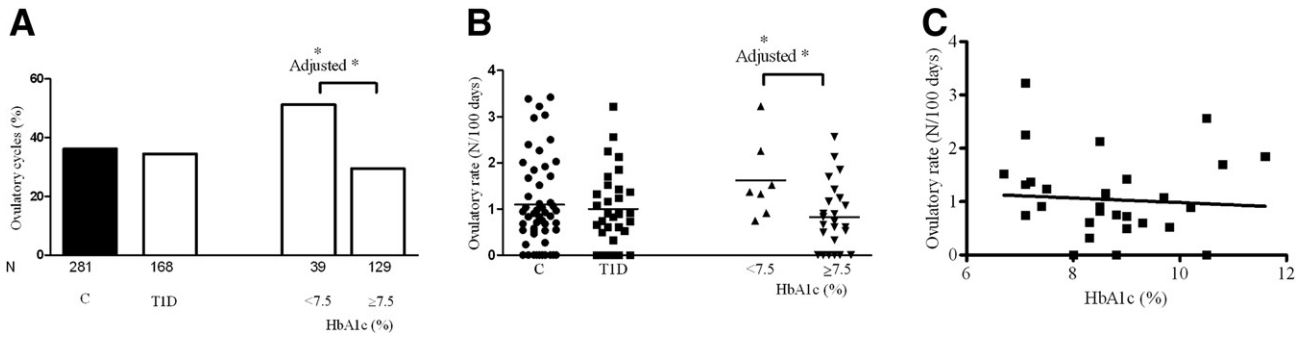
[a] $P<.05$ T1D versus control.

[b] $P<.0001$ T1D versus control.

Codner. Ovulation in type 1 diabetes. Fertil Steril 2011.

FIGURE 1

Ovulation in adolescents with type 1 diabetes (T1D) and in controls, and the relationship with optimal metabolic control in the T1D adolescents.(**A**) Proportion of ovulatory cycles. Unadjusted analysis was performed with Pearson's chi-square test. The number of cycles studied in each group is shown below each bar. *P=.012, adjusted P=.04. (**B**) Ovulatory rate. *P=.02, adjusted P=.04. (**C**) Correlation of ovulatory rate with hemoglobin A1c (HbA1c) levels ($r = -0.13$, P=.5).



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during the follow-up period. The hormone study is shown in the Supplemental Table 1 (available online). Higher SHBG and lower 17OHP levels were observed in the patients with T1D, but the remaining steroid and gonadotropin levels were similar in both groups.

A similar proportion of ovulatory cycles was observed in the T1D and control girls (34.5% and 36.3%, respectively; Fig. 1A) during all the gynecologic periods studied (Table 2). The proportion of girls who did not have any ovulatory cycles was similar in both groups (19.4% and 19.2% in the T1D and control girls, respectively). Maximum salivary progesterone levels in ovulatory cycles were 0.1 ± 0.04 and 0.2 ± 0.4 ng/mL in the T1D and control groups (P=.079). Logistic regression showed that gynecologic age (P<.0001; B = 0.034; standard error of the mean = 0.008), but not T1D or BMI, was a determinant factor for the rate of ovulation.

Ovulatory rate was similar in the T1D and control groups (1.0 ± 0.8 and 1.1 ± 1.0 ovulatory cycles/100 days, respectively; see Fig. 1B) during the different periods that were studied (Table 2). A similar proportion of the T1D and control groups were oligo-ovulatory, defined as fewer than 1 ovulation every 100 days (58.1 and 59.6%, respectively). Mixed generalized equation estimation methodology showed that T1D was not a determining factor over ovulatory rate (P=.94), but that gynecologic age was associated with a higher ovulatory rate (P=.008).

The proportion of ovulatory cycles according to the degree of metabolic control is shown in Figure 1. Girls with optimal metabolic control had a higher proportion of ovulatory cycles (Pearson's chi-square test, P=.012; adjusted for gynecologic age by logistic regression, P=.042) (see Fig. 1A) and ovulatory rate (Student's t test, P=.02; adjusted for gynecologic age and length of follow-up by multivariate analysis, P=.04) (see Fig. 1B). However, when HbA1c was considered as a continuous variable, no correlation with the rate of ovulation was observed (see Fig. 1C). Similar results were observed whether the most recent HbA1c determination or the average level during the last year were considered. Similar maximum salivary progesterone levels were observed in the ovulatory cycles of girls with optimal and insufficient metabolic control: 0.1 ± 0.03 and 0.1 ± 0.04 ng/mL, respectively.

DISCUSSION

To our knowledge, this is the first study to evaluate ovulation in T1D adolescents. Our results show that young nonhyperandrogenic adolescents with T1D and normal controls have similar rates of ovulation. These results highlight the importance of education regarding pregnancy prevention in adolescent girls with T1D. In addition, our findings indicate that optimal metabolic control is associated with a higher ovulatory rate.

The observation of a normal ovulatory rate in adolescents with T1D is in agreement with data from recent studies showing an improvement in fertility in patients with T1D. In an epidemiologic study, Jonasson et al. (22) showed that women whose T1D was diagnosed before 1985 had lower fertility rates than healthy women, but that the group of women who were diagnosed after 1985 had preserved fertility, with the exception of those with chronic complications. Similarly, we observed a comparable number of pregnancies in a group of adult women with T1D without chronic complications as compared with healthy controls (5).

Our data suggest the presence of preserved ovulation in adolescents with T1D. Studies have shown a similar or even higher number of pregnancies in T1D women younger than 25 years but a lower rate of conceptions among older patients (9, 10). This finding may be explained by factors related to the appearance of chronic complications of diabetes (9) or by early aging of the ovary in women with T1D (6).

The normal ovulatory rate that we observed during the early years after menarche in adolescents with T1D is especially important because these patients have a higher risk of unplanned pregnancy compared with women who have other chronic conditions (11, 12). In addition, these patients have a lower level of education regarding prenatal care (23). Charron-Prochownik et al. (23) recently studied attitudes regarding sexuality and family planning in adolescent girls with T1D. They found that these patients believed that they were only moderately susceptible to becoming pregnant, so most did not exhibit protective family planning behaviors. Unfortunately, once the T1D patient becomes pregnant, she is at a higher risk of complications from pregnancy, as is her newborn (24, 25).

Women with T1D exhibit multiple abnormalities in ovarian function. Menstrual irregularities (8, 26), hyperandrogenism (6, 7), a shorter reproductive span due to delayed menarche, and early menopause have been reported (4). The findings of this study showing a normal ovulatory rate in T1D adolescents without hyperandrogenism should not be extrapolated to other groups of women with T1D, such as those with hyperandrogenism, more severe menstrual irregularities, or older age.

TABLE 2

Ovulation rate, proportion of ovulatory cycles, and follow-up period in adolescents with type 1 diabetes mellitus (T1D) and controls.

	Whole group		Postmenarche year					
			First		Third		Fourth	
	T1D	Control	T1D	Control	T1D	Control	T1D	Control
N	31	52	9	11	13	22	9	19
Time of follow-up (d)	181.2 ± 71.9	186.8 ± 93.7	205.4 ± 68.0	309.7 ± 96.0[a]	170.5 ± 65.5	145.1 ± 52.7	172.3 ± 85.9	163.8 ± 67.9
Cycles studied per subject (N)	5.4 ± 2.3	5.4 ± 2.3	5.4 ± 2.1	7.5 ± 2.7	5.3 ± 2.1	4.5 ± 1.5	5.6 ± 2.9	5.2 ± 2.2
Cycles studied in the group (N)	168	281	49	83	70	100	49	98
Ovulation rate (N/100 d)	1.0 ± 0.8	1.1 ± 1.0	0.7 ± 0.4	0.6 ± 0.4	0.8 ± 0.7	1.1 ± 0.9	1.6 ± 1.0	1.4 ± 1.1
Ovulatory cycles (%)	58 (34.5)	102 (36.3)	13 (26.5)	20 (24.1)	19 (27.1)	37 (37)	26 (53.1)	45 (45.9)

Note: Data are shown as mean ± standard deviation.

[a] $P=.013$ T1D versus control.

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We observed a higher rate of ovulation associated with the presence of optimal metabolic control, which is a new finding and is related to the ISPAD recommendations of a HbA1c <7.5% (18). This observation should stimulate T1D women who want to become pregnant to optimize their metabolic control before trying to get pregnant. On the other hand, we observed a lower ovulatory rate in those girls with insufficient metabolic control compared with those who had satisfactory control, but some of the girls with poor control exhibited two or three ovulatory cycles every 100 days (see Fig. 1B), suggesting a wide ovulatory range in these girls. These data should alert the clinician treating adolescents with T1D that there is a risk of pregnancy regardless of the HbA1c level.

The relationship of metabolic control with ovarian function is highlighted by the fact that several abnormalities become more severe with worsening metabolic control. Recently, we have shown an increase in the prevalence of oligomenorrhea, amenorrhea, and longer menstrual cycle durations in adolescents with higher HbA1c levels, with an increase of the cycle duration of 5.1 days for every point increase in the HbA1c level (8). Similarly, Danielson et al. (27) showed a delay in the age of menarche with increasing HbA1c levels. Age of menarche was delayed in our study, which is similar to the series that have shown a persistence of delayed menarche in girls with T1D even after treatment with multiple insulin doses (2). In our study, menstrual irregularities were observed in 33% and 25% of the T1D and control girls, respectively, which did not reach statistical significance but is in concordance with previous studies showing a high prevalence of menstrual irregularities in adolescents with T1D (8, 26, 28).

The main strength of our study is the prospective follow-up evaluation of ovulation during several menstrual cycles in adolescents with T1D. Our study has several limitations. We did not find a correlation between HbA1c levels, when analyzed as a continuous variable, and the ovulatory rate, which could have been related to girls with HbA1c lower than 7% being excluded from this study. Ovulation was not evaluated beyond day 28 of the menstrual cycle, which represents a limitation of the study although ovulation after this interval is rare. Another potential limitation of this study is the sample size of the groups classified according to gynecologic age; however, we believe this does not represent a limitation because a large number of ovulatory cycles was studied in the entire groups of girls (168 and 281 cycles in T1D and control girls, respectively). A calculation of the sample size employing the proportion of ovulatory cycles observed in our study (34.5% and 36.3%) shows that 14,942 cycles should be studied to find a statistically significant difference.

In conclusion, our study shows adolescent girls with moderately controlled T1D exhibited an ovulatory rate similar to that of the normal controls.

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SUPPLEMENTAL TABLE 1

Hormone profile of adolescent girls with type 1 diabetes mellitus (T1D) and controls.

	Whole group		Postmenarche year					
			First		Third		Fourth	
	T1D	Control	T1D	Control	T1D	Control	T1D	Control
N	31	52	9	11	13	22	9	19
T (ng/dL)	40 ± 10	40 ± 10	30 ± 10	40 ± 20	30 ± 10	40 ± 10	50 ± 10	40 ± 10
A (μg/L)	1.4 ± 0.7	1.3 ± 0.6	1.5 ± 1.0	1.3 ± 0.9	1.2 ± 0.3	1.3 ± 0.4	1.7 ± 0.5	1.5 ± 0.7
DHEAS (ng/mL)	1,072 ± 461	1,252 ± 562	969 ± 362	1,030 ± 612	908 ± 360	1,236 ± 519	1,393 ± 542	1,399 ± 566
SHBG (nmol/L)	62.8 ± 18.9	45.9 ± 14.6[a]	63.4 ± 15.2	46.8 ± 14.8[b]	66.3 ± 21.7	44.7 ± 15.2[c]	57.7 ± 19.1	46.8 ± 14.5
E_2 (pg/mL)	61.1 ± 23.2	53.9 ± 19.3	54.1 ± 11.3	62.3 ± 28	62.6 ± 35.5	50.7 ± 13.3	65.4 ± 15.7	52.8 ± 18.9
FSH (IU/L)	5.4 ± 1.7	5.1 ± 1.8	6.2 ± 2.0	4.9 ± 3.2	4.8 ± 1.6	5.0 ± 1.1	5.4 ± 1.4	5.3 ± 1.3
LH (IU/L)	3.5 ± 2.4	3.5 ± 3.1	3.6 ± 2.2	4.4 ± 4.3	2.7 ± 1.4	2.5 ± 1.3	4.4 ± 3.3	4.1 ± 3.6
17OHP (μg/L)	0.9 ± 0.6	1.4 ± 1.3[c]	1.1 ± 0.8	1.2 ± 0.8	0.9 ± 0.5	1.2 ± 0.4[c]	0.9 ± 0.4	1.8 ± 1.9[b]

Note: Data are shown as mean ± standard deviation. 17OHP = 17-hydroxyprogesterone; A = androstenedione; DHEAS = dehydroepiandrosterone sulfate; E_2 = estradiol; FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex-hormone–binding globulin; T = testosterone. To convert units to SI: T: ng/dL × 0.0347 = nmol/L; A: μg/L × 3.49 = nmol/L; DHEAS: ng/mL × 0.0027 = nmol/L; E_2: pg/mL × 3.67 = pmol/L; 17OHP: ng/mL × 3.03 = nmol/L.

[a] $P<.001$ T1D versus control.

[b] $P<.05$ T1D versus control.

[c] $P<.01$ T1D versus control.

Codner. Ovulation in type 1 diabetes. Fertil Steril 2011.