# Sexual Function and Endocrine Profile in Fertile Women With Type 1 Diabetes

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**OBJECTIVE** — Aims of this study were *1*) to assess sexual function and endocrine profile among fertile type 1 diabetic women during the follicular and luteal phases of the menstrual cycle, *2*) to compare these results with those obtained among healthy fertile women who served as control subjects, and *3*) to explore the correlations between sexual function and endocrine milieu among patients and control subjects during the follicular and luteal phases of the menstrual cycle.

**RESEARCH DESIGN AND METHODS** — Fifty fertile women with type 1 diabetes and 47 healthy control subjects completed a semistructured medical interview and filled in self-administered validated instruments to evaluate sexual function, depression, and sexual distress. Venous blood samples were drawn to measure glycated hemoglobin and an endocrine profile during either the follicular or the luteal phase of the menstrual cycle.

**RESULTS** — Type 1 diabetic women had decreased sexual function and increased sexual distress compared with control subjects during the luteal, but not the follicular, phase of the menstrual cycle. During the follicular phase, patients had lower estrogenic basal tone, lower "weak" androgen (namely $\Delta_4$-androstenedione and dehydroepiandrosterone sulfate) production, and lower free-triiodothyronine and free-thyroxine levels compared with control subjects. During the luteal phase, total testosterone levels were higher in patients than control subjects, while 17β-estradiol and progesterone levels were lower in patients than control subjects.

**CONCLUSIONS** — Among type 1 diabetic women, sexual function and sexual distress vary according to the phase of the menstrual cycle. This finding may have implications on the clinical assessment of sexual function in type 1 diabetic women.

*Diabetes Care* **29**:**312–316, 2006**

Although sexual disorders have been extensively studied in diabetic men (1–4), the sexual function of diabetic women has only recently received attention (4–8). The prevalence of sexual dysfunction in diabetic men approaches 50%, whereas in diabetic women it seems to be slightly lower (5,9,10). Neuropathy, vascular impairment, and psychological complaints have been implicated in the pathogenesis of decreased libido, low arousability, decreased vaginal lubrication, orgasmic dysfunction, and dyspareunia among diabetic women. However, discrepancies exist between different reports (5,8,11). This could result, at least in part, from relatively small sample size, uncontrolled study design, or inaccurate characterization of diabetes. In fact, type 1 and type 2 diabetes seem to differently influence women's sexual function (5,6,12,13). To our knowledge, correlations between sexual function and endocrine profile and phase of the menstrual cycle in type 1 diabetic women have been scarcely investigated.

Aims of the present study were *1*) to assess sexual function and endocrine profile among fertile type 1 diabetic women during the follicular and luteal phase of the menstrual cycle, *2*) to compare these results with those obtained among healthy fertile women who served as control subjects, and *3*) to explore the correlations between sexual function and endocrine milieu among patients and control subjects during the follicular and luteal phases of the menstrual cycle.

## RESEARCH DESIGN AND METHODS

— From March 2001 to April 2004, 50 fertile Caucasian type 1 diabetic women attending our outpatient diabetes clinic were enrolled in this study. Patients were eligible if they *1*) were aged ≥18 years, *2*) had type 1 diabetes on intensive insulin therapy, *3*) were under good pharmacologic control when hypertension was present, *4*) received appropriate replacement (L-thyroxine) or suppressive (methimazole) therapy when thyroid disease was present, and *5*) were free of severe chronic complications of diabetes. Patients were compared with a control group of 47 Caucasian healthy fertile women, aged ≥18 years with regular menstrual cycle, recruited through advertisements within our hospital.

Participants in both groups were eligible if they had been involved in a stable heterosexual relationship for the preceding 6 months and were not on oral contraceptives. The general characteristics of patients and control subjects are reported in Table 1. The study was approved by the local ethical committee, and all participants signed an informed consent before enrollment.

All participants were asked to complete a semistructured interview and to fill in a set of validated instruments, including the Female Sexual Function Index (FSFI) (14), the Female Sexual Distress Scale (FSDS) (15), and the 21-item Beck's Inventory for Depression (BDI) (16). The FSFI is a multidimensional self-report instrument for the assessment of female sex-

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Received for publication 10 June and accepted in revised form 28 October 2005.

**Abbreviations:** BDI, Beck's Inventory for Depression; DHEAS, dehydroepiandrosterone sulfate; FSDS, Female Sexual Distress Scale; FSFI, Female Sexual Function Index; fT3, free-triiodothyronine; fT4, free-thyroxine; SHBG, sex hormone–binding globulin.

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

**Table 1—*General characteristics of study participants variable***

| | Patients ($n$ = 50) | Control subjects ($n$ = 47) | $P$ |
|---|---|---|---|
| Age (years) | 33.5 ± 1.1 | 34.1 ± 1.1 | 0.92 |
| BMI (kg/m$^2$) | 22.0 (20.2–23.4) | 20.4 (19.3–24.5) | 0.17 |
| Previous childbirth | 22/50 (44) | 17/47 (36) | 0.43 |
| A1C (%) | 8.4 (7.5–10.1) | 4.8 (4.1–5.3) | 0.001 |
| Current smokers | 17/50 (34) | 24/47 (51) | — |
| Duration of diabetes (years) | 14.1 ± 1.5 | — | — |

Data are means ± SE, median (1st and 3rd quartile), or *n*/total (%).

ual function that includes 19 items compiled in six domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) (14). The FSDS is a 12-item instrument to measure sexually related distress in women (15), and the BDI is a widely used self-rating scale for measuring depression (16). The scores for each instrument were calculated according to the recommended scoring system (14–16).

A venous blood sample was drawn from each participant to measure $HbA_{1c}$ (A1C) and a hormonal profile including free-triiodothyronine (fT3), free-thyroxine (fT4), thyroid-stimulating hormone, prolactin, follicule-stimulating hormone, luteinizing hormone, total and free testosterone, sex hormone–binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), $\Delta_4$-androstenedione, 17β-estradiol, and progesterone. Samples were drawn between 8 and 10 A.M., according to the National Committee for Clinical Laboratory Standards guidelines (17), and kept at 4°C until serum and plasma were separated by centrifugation at 4°C. Serum and plasma aliquots were subsequently stored at −80°C until assay. To obtain a psychosexual and hormonal profile throughout the menstrual cycle, participants completed the study either during the follicular (days 5–8; $n$ = 25 patients and $n$ = 24 control subjects) or luteal (days 19–22; $n$ = 25 patients and $n$ = 23 control subjects) phase of the menstrual cycle (18). A1C was measured using a high-performance liquid chromatography method. Hormones were measured using radioimmunologic (free testosterone and $\Delta_4$-androstenedione), immunometric (17β-estradiol, DHEAS, SHBG, and thyroid-stimulating hormone), electrochemiluminescence (follicule-stimulating hormone, luteinizing hormone, progesterone, total testosterone, and prolactin) or immunofluorimetric (fT3 and fT4) assays. To minimize interassay variation, samples from patients and control subjects collected during the follicular or luteal phase were randomly arranged in two batches. The average intra-assay coefficient of variation (CV) for all analytes was 5%, and the average interassay CV was 8%.

The participants' medical records were reviewed to abstract data on contraception, comorbidities and use of medications, BMI, and diabetes complications.

### Data analysis

Statistical analyses were performed using Stata 8.2 (StataCorp, College Station, TX). Variables with a skewed distribution (BMI, FSFI [except for the desire domain], BDI, and FSDS scores, all components of the hormonal profile [except fT3 and free testosterone]) are reported as median, with first and third quartile in parentheses. Variables with a normal distribution are reported as means ± SE, unless otherwise indicated. Comparisons between patients and control subjects were performed using the Mann-Whitney test for variables with skewed distribution and the Student's $t$ test for variables with normal distribution. Proportions were compared using Pearson's $\chi^2$ test. Relationships among variables were analyzed using Spearman's correlation coefficient. The level of statistical significance was 0.05.

## RESULTS

### Psychosexual profile

Table 2 details FSFI, BDI, and FSDS scores for patients and control subjects during the follicular and luteal phases of the menstrual cycle. During the 4 weeks before the study, seven patients and none of the control subjects reported having no sexual activity. During the follicular phase, patients and control subjects had similar FSFI scores. However, during the luteal phase, patients had significantly lower FSFI scores than control subjects for the arousal, lubrication, orgasm, and pain domains as well as for the full scale. Based on the BDI scores, patients and control subjects did report similar depressive symptoms during both the follicular and the luteal phases of the menstrual cycle. When a threshold BDI score of ≥17 was used to define depression (16), similar proportions of patients and control subjects were clinically depressed during the follicular and the luteal phases.

According to FSDS scores, sexual distress was similar among patients and control subjects during the follicular phase. However, during the luteal phase, pa-



**Table 2—*FSFI, BDI, and FSDS scores among patients and control subjects during the follicular or luteal phase of the menstrual cycle***

| | Follicular phase | | | Luteal phase | | |
|---|---|---|---|---|---|---|
| | Patients | Control subjects | $P$ | Patients | Control subjects | $P$ |
| FSFI domain | | | | | | |
| Desire | 3.6 (2.4–4.8) | 3.6 (3.0–4.8) | 0.724 | 4.2 (2.7–4.8) | 4.2 (3.6–4.8) | 0.648 |
| Arousal | 5.1 (2.7–5.4) | 4.8 (4.0–5.4) | 0.615 | 4.7 (2.9–5.1) | 5.1 (4.2–5.4) | 0.048 |
| Lubrication | 5.7 (3.9–6.0) | 5.9 (5.6–6.0) | 0.364 | 5.2 (3.4–6.0) | 6.0 (5.4–6.0) | 0.037 |
| Orgasm | 5.6 (2.4–6.0) | 5.4 (5.0–6.0) | 0.710 | 4.6 (2.8–5.6) | 5.6 (4.8–6.0) | 0.036 |
| Satisfaction | 5.6 (4.0–6.0) | 5.2 (4.6–6.0) | 0.782 | 5.0 (2.4–5.6) | 5.6 (4.8–6.0) | 0.055 |
| Pain | 5.2 (3.6–6.0) | 6.0 (4.6–6.0) | 0.560 | 5.0 (4.0–6.0) | 6.0 (5.6–6.0) | 0.003 |
| FSFI all items | 31.1 (19.5–33.0) | 31.0 (26.1–32.6) | 0.976 | 27.8 (20.2–31.4) | 31.1 (28.6–32.7) | 0.015 |
| BDI | 5.0 (2.0–12.0) | 5.5 (0.5–12.5) | 0.489 | 6.0 (4.0–11.0) | 4.0 (1.0–11.0) | 0.166 |
| FSDS | 9.5 (2.0–14.5) | 5.5 (1.0–17.0) | 0.656 | 11.0 (5.0–17.0) | 3.0 (0.0–14.0) | 0.049 |

Data are median (1st and 3rd quartile).

**Table 3—*Hormonal profile among patients and control subjects during the follicular or luteal phase of the menstrual cycle***

| | Follicular phase | | | Luteal phase | | |
|---|---|---|---|---|---|---|
| Variable | Patients | Control subjects | *P* | Patients | Control subjects | *P* |
| Prolactin (μg/l) | 7.8 (6.0–11.8) | 9.9 (6.7–12.2) | 0.276 | 9.4 (6.5–11.4) | 9.5 (6.5–12.6) | 0.445 |
| Follicule-stimulating hormone (IU/l) | 5.5 (3.5–8.01) | 6.0 (4.4–7.1) | 0.522 | 3.9 (2.2–4.7) | 2.9 (1.6–5.7) | 0.845 |
| Luteinizing hormone (IU/l) | 5.18 (3.52–12.03) | 4.69 (3.72–8.02) | 0.638 | 5.86 (2.93–9.13) | 4.63 (1.95–9.58) | 0.734 |
| fT3 (pmol/l) | 3.5 (2.9–4.1) | 4.0 (3.5–4.3) | 0.007 | 3.6 (3.2–3.8) | 3.9 (3.7–4.2) | 0.009 |
| fT4 (pmol/l) | 13.6 (11.7–15.3) | 15.7 (13.9–17.4) | 0.014 | 15.2 (13.2–16.2) | 23.3 (14.7–33.6) | 0.072 |
| Thyroid-stimulating hormone (mU/l) | 1.6 (0.8–2.2) | 1.9 (1.1–2.7) | 0.225 | 1.2 (0.8–2.3) | 1.8 (1.6–2.1) | 0.148 |
| 17β-estradiol (pmol/l) | 138 (79–272) | 354 (256–516) | 0.001 | 380 (202–659) | 576 (499–808) | 0.019 |
| Progesterone (nmol/l) | 1.6 (0.7–3.7) | 2.2 (1.5–2.7) | 0.484 | 3.6 (1.9–27.1) | 43.8 (6.6–20.7) | 0.001 |
| Total testosterone (nmol/l) | 1.7 (1.2–1.9) | 1.3 (1.0–1.8) | 0.121 | 1.9 (1.5–2.5) | 1.6 (1.4–1.9) | 0.048 |
| Free testosterone (pmol/l) | 3.0 (1.8–5.2) | 2.9 (2.1–4.1) | 0.745 | 4.3 (3.0–6.5) | 3.3 (2.0–4.8) | 0.116 |
| SHBG (nmol/l) | 59.4 (36.9–97.8) | 72.3 (49.0–97.0) | 0.678 | 72.8 (56.2–120.0) | 119.0 (98.9–149.0) | 0.055 |
| DHEAS (μ mol/l) | 3.2 (1.9–4.3) | 4.8 (3.0–6.2) | 0.043 | 3.4 (1.9–4.9) | 4.0 (2.8–6.3) | 0.141 |
| $\Delta_4$-Androstenedione (nmol/l) | 3.7 (3.0–5.4) | 5.3 (4.1–9.1) | 0.012 | 5.2 (4.3–6.6) | 6.4 (5.5–7.3) | 0.098 |

Data are median (1st and 3rd quartile).

tients had significantly higher FSDS scores than control subjects.

## Endocrine profile

Table 3 details the endocrine profile of patients and control subjects during the follicular and the luteal phases of the menstrual cycle. Patients and control subjects showed similar follicular and luteal gonadotrophin, prolactin, free testosterone, thyroid-stimulating hormone, and SHBG levels. During the follicular phase, patients had lower estrogenic basal tone, lower "weak" androgen production (namely $\Delta_4$-androstenedione and DHEAS), and lower fT3 and fT4 levels compared with control subjects. As expected, progesterone levels in the follicular phase were low and not different among patients and control subjects. On the other hand, during the luteal phase, total testosterone levels were higher in patients than control subjects, while 17β-estradiol and progesterone levels were lower in patients than control subjects.

## Correlations of sexual function with psychosexual variables and endocrine profile

The correlations between FSFI scores and BDI and FSDS scores are presented in Table 4. During the follicular phase, among patients, an inverse correlation was found between the scores of all FSFI domains and BDI and FSDS scores. Among control subjects the total, desire, and orgasm domain FSFI scores were inversely correlated to the FSDS score. During the luteal phase, among patients, an inverse correlation was found between the desire and arousal domain scores and BDI scores and between scores of all FSFI domains (except lubrication) and the FSDS score. Among control subjects, the total FSFI score and the scores for desire, satisfaction, and pain domains were inversely correlated to the FSDS score.

Among patients during the follicular

**Table 4—*Correlations between FSFI score and BDI and FSDS scores among patients and control subjects during the follicular and luteal phases of the menstrual cycle***

| | | Follicular phase | | | | Luteal phase | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable 1 | Variable 2 | Patients | | Control subjects | | Patients | | Control subjects | |
| | | $r_S$ | *P* | $r_S$ | *P* | $r_S$ | *P* | $r_S$ | *P* |
| FSFI score | BDI score | | | | | | | | |
| Desire | | −0.50 | 0.003 | −0.34 | 0.105 | −0.61 | 0.004 | −0.03 | 0.889 |
| Arousal | | −0.44 | 0.032 | −0.39 | 0.062 | −0.54 | 0.014 | −0.02 | 0.935 |
| Lubrication | | −0.52 | 0.012 | −0.07 | 0.747 | −0.35 | 0.133 | −0.19 | 0.374 |
| Orgasm | | −0.56 | 0.006 | −0.27 | 0.202 | −0.30 | 0.206 | −0.07 | 0.757 |
| Satisfaction | | −0.54 | 0.008 | −0.25 | 0.235 | −0.37 | 0.104 | −0.08 | 0.732 |
| Pain | | −0.53 | 0.009 | −0.01 | 0.952 | −0.29 | 0.208 | −0.11 | 0.630 |
| All items | | −0.54 | 0.007 | −0.37 | 0.075 | −0.43 | 0.059 | −0.04 | 0.865 |
| FSFI score | FSDS score | | | | | | | | |
| Desire | | −0.70 | 0.001 | −0.42 | 0.040 | −0.51 | 0.030 | −0.41 | 0.049 |
| Arousal | | −0.68 | 0.001 | −0.37 | 0.075 | −0.60 | 0.008 | −0.34 | 0.161 |
| Lubrication | | −0.62 | 0.001 | −0.16 | 0.445 | −0.41 | 0.092 | −0.27 | 0.216 |
| Orgasm | | −0.83 | 0.001 | −0.48 | 0.016 | −0.68 | 0.002 | −0.33 | 0.125 |
| Satisfaction | | −0.79 | 0.001 | −0.39 | 0.058 | −0.63 | 0.005 | −0.62 | 0.002 |
| Pain | | −0.77 | 0.001 | −0.26 | 0.225 | −0.74 | 0.001 | −0.55 | 0.006 |
| All items | | −0.85 | 0.001 | −0.53 | 0.007 | −0.72 | 0.001 | −0.41 | 0.049 |

Data are Spearman's rank correlation coefficient ($r_s$) and *P* value.

phase, we observed a significant correlation between total testosterone and the scores of multiple FSFI domains (arousal $r_S = 0.49$, $P = 0.017$; lubrication $r_S = 0.44$, $P = 0.037$; orgasm $r_S = 0.59$, $P = 0.003$; satisfaction $r_S = 0.57$, $P = 0.005$; and total FSFI total score $r_S = 0.58$, $P = 0.006$). Among both patients and control subjects, we did not observe additional correlations between hormones included in our profile and the multiple components of the FSFI.

Among patients, we did not observe a significant correlation between A1C and the scores of any FSFI domains (except for satisfaction during the luteal phase, $r_S = -0.45$, $P = 0.040$) or the total FSFI score. A1C was correlated with testosterone ($r_S = 0.45$, $P = 0.043$) and SHBG ($r_S = 0.44$, $P = 0.04$) during the follicular phase and with progesterone ($r_S = 0.54$, $P = 0.012$) and fT3 ($r_S = 0.64$, $P = 0.002$) during the luteal phase.

**CONCLUSIONS** — Previous reports have shown an increased prevalence of sexual dysfunction among women with type 1 diabetes (5,6,12,19–23). Our data confirm the observation that type 1 diabetes affects several aspects of female sexual function, including arousal, lubrication, satisfaction, orgasm, and pain, but not desire. The present study extends those observations, suggesting that sexual function among type 1 diabetic women varies during the menstrual cycle. In fact, patients had lower FSFI scores compared with control subjects only during the luteal phase, with decreased arousal, lubrication, impaired capability of reaching orgasm, and increased discomfort or pain at sexual penetration. Furthermore, during the luteal phase, diabetic participants showed an increased sexual distress (FSDS scores) compared with control subjects. To our knowledge, this is the first report of an effect of the phase of the menstrual cycle on sexual function in women with type 1 diabetes.

Some reports (20,21,23) suggest that depression is a major determinant of decreased desire and impaired arousability in women. In others, however, the association between sexual function and depression is controversial (4,5,20,22). The discrepancies between reports may be accounted for by different instruments to assess sexual function and depression, different study settings, and heterogeneous patient population, i.e., patients with type 1 and type 2 diabetes combined. In our study, the decreased sexual function observed in type 1 diabetic participants during the luteal phase was not accounted for by an increased mood deflection, since patients and control subjects had similar BDI scores and similar proportion of participants with clinical depression (i.e., BDI score ≥17) throughout the menstrual cycle.

In fertile women, reduced androgen concentrations are associated with female sexual dysfunction (18). In our study, during the luteal phase when diabetic patients had a decreased sexual function, they surprisingly had higher, although within the normal range, total testosterone levels than control subjects. On the other hand, during the follicular phase, when sexual function was similar in patients and control subjects, type 1 diabetic patients had lower, although within the normal range, "weak" androgens (i.e., $\Delta_4$-androstenedione, DHEAS) levels than control subjects.

The results of our correlation analysis also support the finding that sexual functions in type 1 diabetic women may vary during the follicular and luteal phases of the menstrual cycle. Among diabetic patients, sexual function (FSFI scores) and mood (BDI scores) were negatively correlated to all FSFI domains during the follicular phase, but the correlation was limited to the desire and arousal domains during the luteal phase. No significant correlations between sexual function and mood were observed among control subjects. Furthermore, among patients, a positive correlation between sexual function and total testosterone levels was observed only during the follicular phase.

Widom et al. (24) has reported changes in glucose metabolism during the menstrual cycle in type 1 diabetic women, with decreased insulin sensitivity and a larger increment of 17β-estradiol levels during the luteal phase. In our study, patients had lower 17β-estradiol levels than control subjects during both the follicular and luteal phases; however, the 17β-estradiol increment during the luteal phase was similar in patients and control subjects. Furthermore, we found no correlation between A1C levels and FSFI domains, except for satisfaction during the luteal phase. This latter finding confirms a previous report (4) and suggests that poor glycemic control may have a limited impact on sexual function among type 1 diabetic women. Nevertheless, we recognize the possibility that changes in glycemic control that do not affect A1C levels may indeed have an effect on sexual function in these patients.

In conclusion, we showed that Italian type 1 diabetic women have decreased sexual function and increased sexual distress during the luteal phase of the menstrual cycle. Decreased sexual function occurs independently of mood deflections and does not seem to be influenced by glycemic control. The role of the endocrine milieu remains unclear. The finding that among type 1 diabetic women sexual function varies with the different phase of the menstrual cycle may have implications on the clinical assessment of sexual function in these patients.

**Acknowledgments** — This work was presented in part at the International Society for the Study of Women's Sexual Health, Atlanta, Georgia, 28–30 October 2004.

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