Ovarian function and disease activity in patients with systemic lupus erythematosus

S.S. Shabanova[1], L.P. Ananieva[1], Z.S. Alekberova[2], I.I. Guzov[3]

[1]Department of Microcirculation and Inflammation and [2]Department of Systemic Rheumatic Diseases, Institute of Rheumatology, Moscow; [3]Immunology and Reproduction Center, Moscow, Russia.

Abstract

Objective

Menstrual cycle disturbances frequently occur during the onset or in exacerbation periods of systemic lupus erythematosus (SLE), suggesting a possible relationship. The aim of the study is to assess the ovarian function in SLE patients with active disease before the treatment with high doses of glucocorticoids (GC) and cytotoxic agents.

Methods

We evaluated 94 female SLE patients (mean age of 29.2±7.0 years). The mean SLEDAI score was 11.4±8.1. Seventy-nine patients had a current use of GC with a median dose of 10 mg/day (8-15). The other 15 patients were untreated. After examination and blood sample collection 40% of the patients were treated and high doses of GC (>30 mg/day); 68% from this group of patients were treated GC in combination with cyclophosphamide (CYC). Forty healthy women with the same mean age were evaluated as controls. A careful gynecological history and a gynecological examination were carried out in patients and controls. Hormonal serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol (E2) and progesterone in SLE patients and controls were measured by enzyme-linked immunosorbent assay (ELISA).

Results

Menstrual cycle disorders with oligomenorrhea as dominant aspect were observed in 54% of SLE patients. The hormonal studies showed decreased progesterone level in 52% of patients, reduced E2 concentration in 25% of patients; increased levels of LH, FSH and prolactin were observed with the lower frequency (13%, 9%, 10% respectively). Menstrual cycle disorders and the hormonal unbalance such as decreased progesterone level and hyperprolactinemia were found related significantly to high SLEDAI score ($p<0.05$, $p=0.001$, $p<0.05$). In the group of non-treated SLE patients the menstrual and hormonal disorders were observed in the same spectrum and with the same frequency as in all the examined SLE patients. SLEDAI score was found correlated significantly with the frequency of menstrual cycle disorders in non-treated SLE patients ($p<0.05$).

Conclusion

The reported study shows the disease activity as a major factor associated with menstrual cycle disorders in SLE patients before treatment with alkylating agents and high doses of GC. Therefore, SLE women might be considered as a risk group for altered ovarian function.

Key words

Systemic lupus erythematosus, ovarian function, disease activity.

Sabina S. Shabanova, MD, PhD, Research Associate; Lidia P. Ananieva, MD, Professor of Rheumatology; Zemfira S. Alekberova, Professor of Rheumatology; Igor I. Guzov, MD, PhD, Gynecologist.

Please address correspondence and reprint requests to:
Dr. Sabina S. Shabanova, Kravchenko Street 4-1-54, 119313, Moscow, Russia.
E-mail: Sabina.shabanova@hotmail.com

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Introduction

Systemic lupus erythematosus (SLE) is an acute and chronic autoimmune inflammatory disease known for its female predilection and peak incidence during the reproductive years (1).

Altered neuroendocrine immune interactions could pay an important role in the pathogenesis in SLE and might predispose to an increased susceptibility to the development of the disease. In additional, regardless of the premorbid reactivity of the hypothalamic-pituitary-adrenal (HPA) axis, chronic inflammation itself could alter HPA axis responses (2). Inflammation is accompanied by raised levels of cytokines like interleukin IL6, interleukin IL1, tumor necrosis factor TNF-α that can activate HPA axis (3). The stimulated HPA axis regulates immune responses through the immunosuppressive effects of glucocorticoids (4, 5). Cutolo *et al*. showed that complex interactions occur between the endocrine, nervous and immune systems during synovitis that will potentially uncover new mechanisms in the pathophysiology also of rheumatoid arthritis (6, 7). In addition, SLE and polymyalgia rheumatica might also be characterized by impaired function of the HPA axis, including its altered negative-feedback regulation or reduced cortisol effects owing to glucocorticoid receptor defect (8, 9).

Despite the fact that fertility in the most patients is preserved, the gonadal function of women with SLE can be altered by several factors such as: autoimmunity, disease activity, hyperprolactinemia, dysfunction of the hypothalamic-pituitary-ovarian axis and thyroid, using very high doses of immunosuppressive agents, particularly cyclophosphamide (CYC) and glucocorticoids (GC).

Recent reports suggest that menstrual disturbances varying from menorrhagia to amenorrhea are common in SLE women (10-18). Most of the studies are devoted to the influence of CYC on the gonadal function, since ovarian failure is a well-known side effect of CYC therapy, with older patients being more susceptible (18-20). Anti-ovary autoantibodies, including anti-corpus luteum antibody have recently been demonstrated as markers of autoimmune ovarian failure in SLE (21-23).

Menstrual cycle disturbances frequently occur during the onset or in exacerbation periods of SLE, suggesting a possible relationship. Nevertheless, there are different opinions about the disease activity influence on ovarian function. Some studies stressed the relationship between SLE activity and menstrual cycle disturbances in the other studies this fact was not confirmed (12-16). Furthermore, the distinct role of the disease activity and the GC therapy in menstrual cycle disorders has not been properly evaluated, because these two factors usually occur concomitantly. Having a suppressive effect on the hypothalamic-pituitary-ovarian system, GC induce a decrease of LH and FSH levels (24, 25). Most likely, the ovarian failure in SLE has a difficult genesis.

The aim of the study is to assess the ovarian function of SLE patients with active disease before treatment with high doses of GC and cytotoxic agents, since the above-mentioned relationship was not thoroughly investigated.

Patients and methods

We evaluated 94 consecutive patients with the mean age of 29.2±7.0 years (age range 16-45 years), who had four or more American College of Rheumatology (ACR) criteria for SLE (26), attending the Institute of Rheumatology from Russia during the period from 2001 to 2004.

The exclusion criteria for the study were: pregnancy, lactation, menopause, primary amenorrhea, previous history of hysterectomy, oophorectomy and a current use of oral contraceptive agents.

The mean disease duration was 7.3±6.2 years. The disease activity was measured by the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) (27). The mean SLEDAI score was 11.4±8.1 (range 2-41 balls). All the patients were examined in the period of SLE flare or at the disease onset before the treatment of CYC and high dose of GC. At the time of investigation 79 (84%) patients had a current use of GC with a median dose of 10 mg/day (8-15). The other 15 (16%) patients were

untreated. After examination and blood sample collection 40% of all the patients were treated and high doses of GC (>30 mg/day), 68% of this group of patients were treated with GC in combination with CYC.

Forty healthy women with the same mean age of 28.7±4.4 years (age range 19-41 years) were evaluated as controls. A careful gynecological history (according to the special questionnaire) and physical examination by an attending gynecologist were carried out in patients and controls.

Determination of hormonal serum levels

Blood samples for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL) were collected at the follicular phase (on days 3-7 of menstrual cycle) and for estradiol (E2) and progesterone at the luteal phase (on days 20-22 of menstrual cycle).

Hormonal levels in patients and controls were measured by enzyme linked immunosorbent assay (ELISA). E2 was measured using a commercial kit from DRG Diagnostics (USA); the other hormones were determined by an ALKOR-BIO kit (Russia).

Menstrual disorders were classified as:

- Amenorrhea: the absence of menstrual periods for six and more months
- Oligomenorrhea: menstrual periods occuring at intervals of greater than 35 days.
- Polymenorrhea: menstrual periods occuring at interval of 21 days or fewer.
- Hypomenorrhea: a diminution of the flow or a shortening of the duration of menstruation.
- Hypermenorrhea: heavy or prolonged menstruation.
- Metrorrhagia: bleeding at irregular intervals, particularly between the expected menstrual period.
- Dysmenorrhea: painful menstruation.

Statistical analysis

The data were analyzed by Statistica (StatSoft - Russia, 1999). To determine the average criteria we used M±s in normal dissemination and Me (LQ-UQ) in the dissemination different from normal characteristics. The Mann-Whitney U-test was used to compare two independent groups, and Wilcoxon test to dependent groups. Spearman criterion was used to establish the correlation between the two characteristics. Fisher exact test, Yates corrected χ^2, McNemar χ^2 were used to compare the binary characteristics. In all the statistical tests the level of significance was set at $p<0.05$.

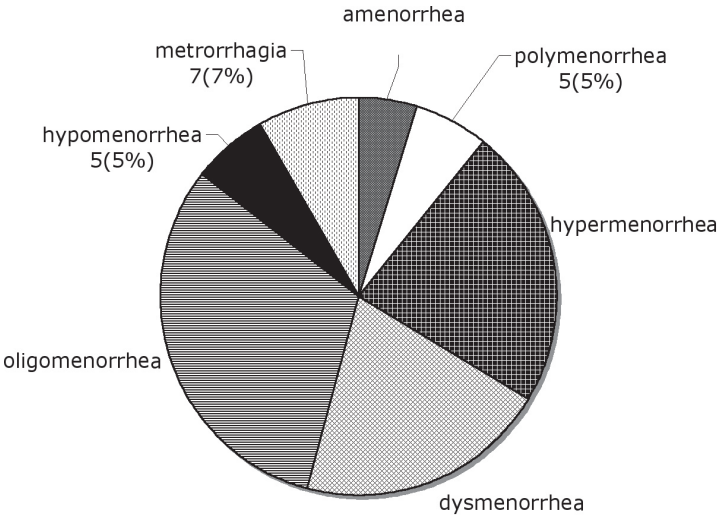

Fig. 1. Frequency of menstrual disturbances in SLE patients.

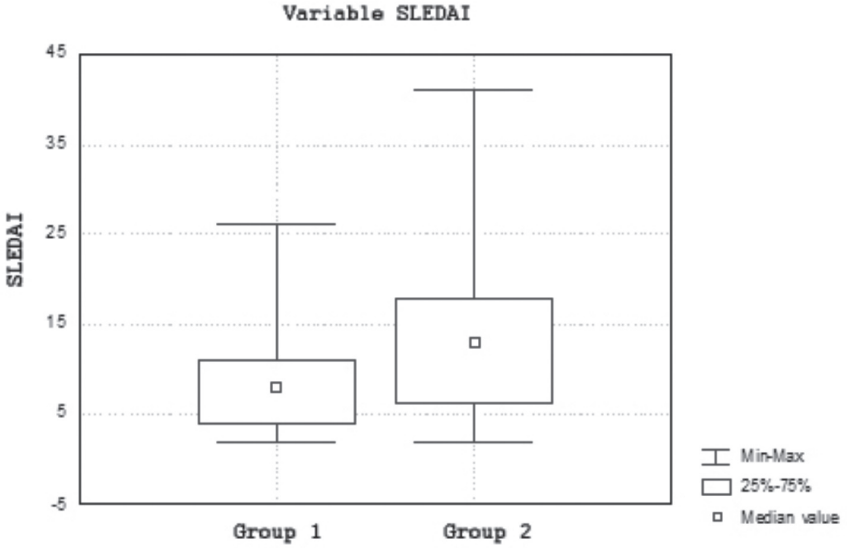

Fig. 2. SLEDAI score in SLE patients with normal menstrual cycle (group 1) and with menstrual disorders (group 2).

Results

Menstrual function

The mean age of menarche in SLE patients was 13.2±1.3 years (range 10-17 years); in 77% of patients, menarche was between 12 and 14.

The mean length of menstrual cycle and blood flow in SLE patients with preserved menstrual cycle were such as in the general population (28±3 and 5±2 days, respectively).

Nevertheless, menstrual cycle disorders with oligomenorrhea dominant were observed in 54% of SLE patients, mainly at the periods of SLE flare or at the disease onset (Fig. 1). There were found associations of menstrual disorders with disease activity. Figure 2 shows that SLEDAI score was significantly higher in the patients with menstrual disorder than in the patients with normal menstrual cycle (14.0±8.9 versus 8.4±5.8 balls, $p<0.001$).

Table I. The mean hormone levels of and SLEDAI score.

	LH (mIU/ml)	FSH (mIU/ml)	PRL (mIU/ml)	E2 (nmol/l)	Progesterone (nmol/l)
SLE patients n=94	3.8 (2.4-5.5)	5.15 (4-7)	374 (272-563)	0.37 (0.23-0.57)	10.9 (2.34-25)*
Group I (SLEDAI <11) n=48	4.1 (3.2-6.5)	5.3 (4.0-8.9)	347 (263-486)**	0.35 (0.25-0.56)	16.2 (4.6-30.9)**
Group II (SLEDAI ≥11) n=46	3.5 (2.1-4.9)	5.0 (3.7-6.0)	450 (275-675)**	0.39 (0.23-0.57)	7.3 (1.1-18.6)**
Control group n=40	3.5 (2.8-6.5)	6.0 (5.0-7.0)	344 (227-438)	0.53 (0.30-0.70)	24.9 (12.6-60)*

*Differences between SLE pts and the control group ($p<0.05$)
**Differences between group I and group II ($p<0.05$)
Normal levels of hormones: LH = 1.1-8.7 mIU/ml, FSH = 1.8-11.3 mIU/ml, PRL = 67-726 mIU/ml (follicular phase); E2 = 0.2-0.8 nmole/l and progesterone = 12.7-79.5 nmol/l (luteal phase).

Hormonal status

The mean levels of LH, FSH, PRL and E2 were comparable among patients and controls. The progesterone levels in SLE patients were significantly lower than in controls ($p<0.05$) (Table I). The hormonal studies showed in 52% patients reduced progesterone, in 25% reduced E2 levels. Increased levels of LH, FSH and PRL were observed with the lower frequency (13%, 9%, 10% respectively) and only 2% of patients had increased E2 concentration. The SLE duration was correlated with LH ($r=0.35$, $t=3.58$, $p<0.05$) and FSH levels ($r=0.21$, $t=2.1$, $p<0.05$).

The patients were divided into two groups according to the SLEDAI score; the first group with the score <11 and the second group with the score ≥11, as the mean SLEDAI score was 11.4±8.1. The average meanings of the age, disease duration and daily steroidal doses were compared in both groups. As shown in Table I, we observed significantly decreased progesterone and increased prolactin in patients with SLEDAI score ≥11 compared with patients having activity <11 balls and controls.

Thus, the decrease of progesterone concentration was the most frequent among the other disorders of hormonal profile. We compared the activity according to SLEDAI score in patients with the normal (n=45) and the decreased progesterone levels (n=49). In the patients with a low level of progesterone the SLEDAI score was significantly higher than in the patients with normal progesterone concentration (14.0±9.0 *vs*. 8.5±5.7 balls, $p=0.001$). The SLEDAI score in the patients with hyperprolactinemia (10%) was significantly higher that in the patients with the normal PRL levels (16.0±7.4 *vs*. 10.7±7.9, $p<0.05$). No statistically significant difference between the other hormone levels and the SLEDAI score was observed.

Therefore, the frequency of menstrual disorders in the SLE patients correlated with decreased progesterone ($r=0.47$, $t=5.0$, $p<0.001$) and E2 levels ($r=0.23$, $t=2.2$, $p<0.05$).

As most of the SLE patients (84%) were taking GC, it is necessary to stress the influence of this therapy on the ovarian function. Mean daily GC doses were similar in the patients with and without menstrual disturbances (12 (8-24) versus 8 (8-12) mg/day). LH and FSH lowering which may be due to GC therapy was not confirmed in our study.

The state of ovarian function in non-treated SLE patients is of great significance, because it allows us to evaluate properly the distinct role of the disease activity on menstrual cycle disorders.

In our study, 9 out of 15 (60%) patients without GC therapy had menstrual disturbances. SLEDAI score correlated significantly with the frequency of menstrual disorders in non-treated SLE patients ($r=0.75$, $t=4.1$, $p=0.001$). Moreover, progesterone deficiency, tendency to decrease of E2 levels, increase of LH, FSH and prolactin levels in patients without GC therapy were noted with the same frequency as in all the investigated SLE patients.

Thus, the ovarian function in SLE patients is more correlated to the disease activity, than to the GS therapy.

Discussion

The reported study shows the disease activity as a major factor associated with menstrual cycle disorders in SLE patients before the treatment of alkylating agents and high doses of GC.

It is noteworthy that patients over 45 years old were systematically excluded. Moreover, other gynecological causes of menstrual disturbances such as previous history of oophorectomy, hysterectomy and recent uterine curettage were avoided by our selection criteria. Likewise, patients with hormonal changes due to pregnancy or in the lactation period and those consequent to the use of oral contraceptive agents were not included. Importantly, that in our study the patients' examination was performed before giving them adequate immunosuppressive therapy.

Different menstrual disorders were observed in 54% of SLE women, and most of them showed progesterone deficiency (52%). In fact, mean progesterone level in SLE patients was significantly lower than in the controls. Our results are similar to the other studies con-

cerning decreased progesterone level, which might exert an immunosuppressive effect in SLE patients (28-31).

It is well known, the feature of sexual hormone metabolism in SLE having a hyperestrogenic trend. (32-35). In patients with SLE the aromatic hydroxylase activity was found increased, that may partially explain the abnormalities of peripheral estrogen metabolism observed in these patients (35, 36). According to Lahita, lupus patients have an increased 16α-to-2α hydroxylated estrogen metabolite ratio, resulting in the production of more "feminizing" estrogens (37-39). Concerning E2, its levels were reported to be in increased, normal, or low in SLE patients (1, 28, 31). In our study, the decrease of E2 level was dominant and only in 2% of patients its increase was observed. An investigation from Munoz *et al*. (31) obtained the similar results: in SLE women during luteal phase of menstrual cycle progesterone and E2 levels were decreased.

Many surveys have shown that PRL level is increased in SLE patients. According to different studies (40-43), the prevalence of hyperprolactinemia in SLE patients fluctuates between 2 and 40%. We observed mild hyperprolactinemia in 10% of SLE patients.

Remarkably, menstrual cycle disorders and the hormonal imbalance such as decreased progesterone level and hyperprolactinemia were related significantly to high SLEDAI score. Our results are similar the other studies that also showed the dependence of menstrual disorders in SLE patients on disease activity (12, 13, 17). Association of hyperprolactinemia with high SLE activity was already found in other investigations (44-47).

Recent data have suggested that SLE is associated with dysfunction of the HPA axis (48). Dysfunction of HPA was found in moderately active SLE. Furthermore, in relation to the level of interleukin 6 (IL-6) or tumor necrosis factor (TNF), cortisol was clearly low compared with controls. According to Koller *et al*. the HPA axis appeared to be unaffected, but the pituitary-thyroid and pituitary-gonadal axes were disturbed among the SLE patients at (or before) the onset of disease (49). In our study the elevation of FSH and LH concentration that is an early marker of ovarian damage was revealed with low frequency – 13 and 9%, which may be result of the ovarian functional reserve reduction.

The prolonged use of GC therapy is characteristic of SLE and high doses of it can also cause oligomenorrhea or amenorrhea in female patients (50). According to our results, mean daily GC doses did not significantly differ in patients with and without menstrual disturbances. Therefore, we may suppose that low GC doses do not have negative effect on ovarian function. Pasoto *et al*. obtained similar results; in that study the use of non-high prednisone doses (10-20 mg/day) in SLE patients did not cause significant disorders of ovarian function and suppression of gonadotropin secretion (13).

The decrease of serum progesterone levels, observed with the highest frequency in SLE, suggest luteal phase dysfunction and anovulatory menstrual cycles. The unbalance of steroidal hormones in the organism may result in endometrial hyperplasia, dysfunctional uterine bleeding, disease of mammary glands (mastopathia) and others.

Considering the risk of endometrial hyperplasia in SLE patients with ovarian failure, they possibly should use low-doses progestin-containing contraceptives. Such problems as pregnancy planning, contraception methods and gynecological treatment should be discussed with gynecologists. In conclusion, SLE patients might be considered as a risk group for altered ovarian function.

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