Prevalence and risk factors for menstrual disorders among systemic lupus erythematosus patients

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ABSTRACT

Introduction: This study aims to determine the prevalence and the types of menstrual disorders among patients with systemic lupus erythematosus (SLE) and to identify factors that influence their development.

Methods: 61 patients with SLE were enrolled into a cross-sectional, observational study at the medical outpatient clinic, Hospital Universiti Sains Malaysia. A total of 120 healthy women were selected randomly to act as the control group. A questionnaire was administered, vital signs were recorded, and blood was evaluated for routine investigations. A review of past medical records was also undertaken.

Results: The mean age and standard deviation for the study group was 33.23 +/- 10.96 years, the majority being ethnic Malays. 75 percent had a severe SLE disease activity index score on initial presentation, and 59 percent were on cyclophosphamide. 49 percent of the study population had menstrual irregularities, of which 60 percent had sustained amenorrhoea. Nine patients with sustained amenorrhoea had hormonal assays, which confirmed the diagnosis of premature menopause.

Conclusion: This study showed that SLE patients had a higher risk of developing menstrual irregularities compared to the normal/healthy population. The risk was higher in the older age group (greater than 30 years old) and those on cyclophosphamide therapy, especially those with a cumulative dose of more than 10 g. Sustained amenorrhoea was the commonest irregularity and a majority of them had confirmed premature menopause.

Keywords: amenorrhoea, menstrual disorders, premature menopause, systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by circulating autoantibodies and immune complexes, and has diverse manifestations.[1] 80% of SLE occurs in women of child-bearing age,[2] of which the commonest age group is between 20 and 40 years.[3] It is also within this age group that women have regular and persistent patterns of menstrual cycle length, with little variation individually.[4] On the other hand, nearly every woman will experience at least one or more menstrual disorders in her life time, the most common being amenorrhoea.[5] Sustained menstrual disorders, however, are fairly common in SLE patients.[6] They range from increased cycle flow, oligomenorrhoea, temporary amenorrhoea and sustained amenorrhoea (secondary to ovarian insufficiency). The main factors which have been associated with the onset of ovarian failure in patients diagnosed with SLE are disease activity,[6] anti-ovarian antibodies[7,8] and cytotoxic agents.[9,10] SLE is also associated with premature ovarian failure in which ovarian follicles with seemingly normal oocytes fail to grow and ovulate in the presence of elevated gonadotrophins.[11] Cytotoxic agents, such as cyclophosphamide, also cause premature follicular depletion via an accelerated rate of follicular atresia or destruction.[11]

SLE is an autoimmune disease which mainly affects women of reproductive age.[2] Menstrual disorders are regarded as common complications in SLE patients.[9,10] Yet, there is no local data or literature discussing menstrual disorders in SLE patients in Malaysia in general, and the state of Kelantan specifically. Therefore, this study was conducted to determine the prevalence of menstrual disorders among those with SLE vis â vis the healthy population, to define their patterns, and to identify factors that influence their development. This knowledge will allow doctors to prepare the patients prior to the initiation of therapy and to offer risk reduction alternatives to the management plan.

METHODS

Patients with SLE who attended the medical outpatient clinic at the Hospital Universiti Sains Malaysia were recruited into this cross-sectional, observational study.

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Table I. Baseline characteristic of the study population.

Characteristic	Frequency (%) (n = 61)
Age (years)	
≤ 20	8 (13.1)
21–30	19 (31.1)
31–40	15 (24.6)
41–50	16 (26.2)
≥ 51	3 (4.9)
Ethnicity	
Malay	56 (91.8)
Non-malay	5 (9.2)
Occupation	
Unemployed	45 (73.8)
Unskilled	9 (14.7)
Skilled	4 (6.6)
Professional	3 (4.9)
Systolic BP (mmHg)	
< 120	1 (1.6)
120–129	9 (14.8)
130–139	17 (27.9)
140–159	26 (42.6)
≥ 160	8 (13.1)
Diastolic BP (mmHg)	
< 80	16 (26.2)
80–85	20 (32.8)
85–89	11 (18.0
90–99	12 (19.7)
≥ 100	2 (3.3)
BMI (kg/m^2)	
< 18.5	10 (16.3)
18.5–22.9	22 (36.1)
23.0–27.4	22 (36.1)
≥ 27.5	7 (11.5)
Creatinine (umol/L)	
< 50	1 (1.6)
50–99	49 (80.4)
100–149	10 (16.4)
≥ 150	1 (1.6)

The study protocol was approved by the medical research and ethics committee of the institution, and written informed consent was obtained from all subjects. Patients fulfilling the American College of Rheumatology (ACR) 1982 revised criteria for SLE, aged between 15 and 50 completed years, were enrolled into the study. These patients were premenopausal and consented to the interview. Details of the patients' menstrual history were obtained by medical officers who were not the principal investigators. The menstrual history was then recorded in the study form. The interviews were carried out in the Malay and English languages, based on the patients' preference.

A total of 120 healthy women were selected randomly to act as the control group. The normal cohort was also premenopausal, did not have primary amenorrhoea and was not pregnant at the time of the interview. Menstrual histories obtained from participants included: age at menarche, duration of heavy bleeding, duration of menses and menstrual cycle (premorbid, during inactive and active SLE, pre-induction, during induction, during maintenance and post-maintenance with cyclophosphamide therapy). Patients who did not satisfy the ACR criteria, had primary or secondary amenorrhoea from a known cause and post-menopausal women were excluded from the study. Males and patients who did not consent to the interview were also excluded.

Patients' blood pressure, height, weight, body mass index (BMI) and other clinical parameters indicative of lupus activities, were reviewed by the attending doctors. The SLE disease activity index (SLEDAI), a validated index used to measure disease activity, was then calculated.[12] Patients' records were reviewed and data was then collected. Laboratory results during initial presentation and follow-up, which included: full blood count, renal function test, liver function test, fasting lipid level, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, double-stranded DNA, complement level (C_3C_4), prolactin, follicle stimulating hormone, luteinising hormone, urine microscopy and 24-hour urine protein, were collected. The patients' medications, which included immunosuppressive therapy such as steroids, cyclophosphamide, azathioprine and cyclosporine A, were noted, and the use of other adjunctive medications were also recorded.

Normal menstrual pattern referred to the normal menstrual pattern in our healthy control group. The duration of heavy bleeding was between two and three days, duration of each menses was between five and 13 days, and the menstrual cycle was between 21 and 35 days. Menarche was defined as the first menstrual period. Oligomenorrhoea was defined as menses occuring at intervals longer than 35 days. Secondary amenorrhoea was defined as the cessation of menses after menstrual cycle has begun and lasted for at least four months for patients with regular cycles, or for at least three of the previous three cycle intervals for patients with irregular cycles.[4] Transient amenorrhoea was defined as when patients resumed her own "normal" cycle after episodes of amenorrhoea, and sustained amenorrhoea was when the patient remained amenorrhoeic until the interview date.

Data for continuous, closely symmetrical variables were analysed using standard descriptive methods to estimate the means ± standard deviation (SD). The sample was described according to sociodemographical data, SLEDAI score, lupus nephritis classes, treatment received and menstrual pattern. Simple logistic regression was used to determine association between menstrual disorders and each independent variable. Multivariate logistic regression models were then computed with menstrual disorders as the outcome. In each model, selection of variables was checked by variance inflation factors, which were obtained by fitting the data in multiple linear regression models. All possible two-way or first-order interactions between significance predictors were checked by the likelihood ratio test. Model fitness was assessed through the use of receiver operating characteristic curve, Hosmer-Lemeshow goodness-of-fit-statistic and classification

Table II. Demographical and clinical characteristics of patients with normal and abnormal menstrual patterns.

Characteristic	Menstrual pattern (Mean ± SD)		p-value
	Normal (n = 31)	Abnormal (n = 30)	
Age (years)	30.94 ± 1.96	35.87 ± 1.90	0.076
SBP (mmHg)	133.23 ± 2.16	140.00 ± 2.53	0.018
DBP (mmHg)	80.65 ± 1.85	88.55 ± 2.06	0.060
BMI (kg/m^2)	22.53 ± 0.64	24.03 ± 0.53	0.079
SLEDAI	17.26 ± 1.82	18.42 ± 1.51	0.626
Lupus nephritis*	1.00 ± 4.00	4.00 ± 1.00	0.001
Haemoglobin (g/dL)	9.30 ± 0.38	9.9 ± 0.32	0.234
White cells (/mcL)	6.94 ± 0.67	6.62 ± 0.63	0.313
Platelets (×10^6)	217.74 ± 15.93	240.97 ± 13.79	0.275
Creatinine (mmol/L)	81.19 ± 4.60	81.32 ± 4.70	0.984
Proteinuria (g/day)	1.18 ± 0.28	1.32 ± 0.21	0.652
C_3 (mg/dL)	0.67 ± 0.07	0.51 ± 0.04	0.063
C_4 (mg/dL)	0.16 ± 0.02	0.19 ± 0.03	0.550
Cholesterol (umol/L)	4.79 ± 0.07	4.96 ± 0.09	0.290
Age at menarche (years)	12.84 ± 0.19	12.87 ± 0.20	0.908
Age at diagnosis (years)	23.74 ± 1.73	27.39 ± 1.67	0.135
Disease duration (years)	6.90 ± 0.64	8.45 ± 0.71	0.113

*Value is expressed in median ± SD

Table III. Prevalence of menstrual disorders in relation to stages of SLE.

Stages of SLE	No. of patients (%) (n = 61)		
	Normal menses	Abnormal menses	
		Oligomenorrhoea	Amenorrhoea
Premorbid	61 (100)	0 (0)	0 (0)
Active phase	48 (78.7)	11 (18.0)	2 (3.3)
Inactive phase	31 (50.8)	13 (21.3)	17 (27.9)

table. The Statistical Package for the Social Sciences version 11.0 (SPSS Inc, Chicago, IL, USA) was used to perform the analysis.

RESULTS

From the study, the mean age and SD was 33.0 ± 10.6 years, mean age and SD of menarche was 12.1 ± 0.8 years, and mean duration of menstrual cycle and SD was 29.3 ± 4.2 days. Of those selected, 100 had a normal menstrual pattern and 20 had episodes of abnormal menstrual patterns at least once in their lives (20/120, 16.7%). The abnormal menstrual patterns were transient oligomenorrhoea (15/120, 12.5%) and transient amenorrhoea (5/120, 4.2%). These patterns were observed during the first few months to one year after attaining menarche. Other related factors observed during episodes of menstrual disorders were emotional stress, excessive physical activity, and a history of taking oral contraceptive pills or on intrauterine devices.

The demographical and clinical characteristics of the study population are shown in Tables I and II. The patients' age was noted in terms of "completed years". The range was 16–51 completed years, with a mean age of 33.2 ± 10.9 years. The median age was 32 years, with a majority of them (55.7%) in the 21–40 years age range. An absolute majority were Malays (91.8 %), while the rest were Chinese and Siamese patients. This was in keeping with the general population demographics of rural Malaysia and that of Kota Bharu, Kelantan, specifically. The majority of those studied were unemployed (73.8%). A majority of SLE patients (83.6%) had high normal to hypertensive range of systolic blood pressure, and 41.0% had high normal to hypertensive range of diastolic blood pressure. Almost half of the patients (47.6%) were overweight, 36.1% of them being pre-obese (BMI range 23.0–27.4 kg/m^2) and another 11.5 % of them being obese (BMI > 27.5 kg/m^2). Most of the patients (82%) had normal serum creatinine.

75.4% (46/61) of patients presented initially with severe SLEDAI score of > 10, whereas only 24.6% of patients had mild to moderate disease activity. However, during the time of the interview, all patients were in a stable and inactive disease state with a SLEDAI score of less than 10. 70.5% (43/61) of the study population had renal biopsies. The commonest lupus nephritis seen was class IV lupus nephritis at 72.1%, 13.9% of patients had class III, 9.3% had class II, 2.3% had class I, and another 2.3% had class V lupus nephritis. None of the patients had class VI lupus nephritis. In this study, 65.6% (40/61) of patients received a combination of steroid and another

Table IV. Prevalence of menstrual irregularities in relation to the cyclophosphamide phases.

Phases of cyclophosphamide therapy	No. of patients (%) (n = 36)		
	Normal menses	Oligomenorrhoea	Amenorrhoea
Pre-induction phase	27 (75.0)	7 (19.4)	2 (5.6)
Induction phase	24 (66.7)	9 (25.0)	3 (8.3)
Maintenance phase	15 (41.7)	12 (33.3)	9 (25.0)
Post-maintenance	11 (30.5)	10 (27.8)	15 (41.7)

Table V. Prevalence of menstrual irregularities in relation to the cumulative dose of cyclophosphamide therapy.

Type and dose of cyclophosphamide therapy	No. of patients (%) (n = 25)		
	Oligomenorrhoea	Transient amenorrhoea	Sustained amenorrhoea
Oral (6.75–10.5 g)	0 (0)	0 (0)	0 (0)
Standard induction (10.5–12.1 g)	10 (40)	1 (4)	11 (44)
Extended induction (> 12 g)	0 (0)	0 (0)	3 (12)

type of immunosuppressive therapy, whereas 34.4% of patients received steroid therapy alone. Among patients who had combination immunosuppressive therapy, the majority of them (90.0%) were on cyclophosphamide, 5.0% of patients were on azathioprine and another 5.0% were on cyclosporine A.

49.2% of SLE patients had menstrual disorders. SLE patients had a three times higher risk of developing menstrual disorders compared to the normal healthy population (49.2% vs. 16.7% in healthy controls). 60% of patients with menstrual disorders had sustained amenorrhoea, followed by oligomenorrhoea (37%) and transient amenorrhoea (3%). The majority of SLE patients with menstrual disorders (76.7%, 23/30) were between 31 and 50 years of age. Premorbidly, all SLE patients had a normal menstrual cycle. During the active phase of SLE, 13 patients (21.3%, 13/61) had menstrual disorders. This included patients who were not on cyclophosphamide therapy, and patients who were at pre-induction and induction phases of cyclophosphamide therapy. The major menstrual disorder at this stage was oligomenorrhoea. During the inactive phase of SLE, 30 patients (49.2%) had menstrual disorders. This included patients who were not on cyclophosphamide therapy, and patients who were at maintenance and post-maintenance phases of cyclophosphamide therapy. 13 patients (21.3%) had oligomenorrhoea and 17 (27.9%) had amenorrhoea. Among patients who had amenorrhoea, only one patient had transient amenorrhoea, while the rest had sustained amenorrhoea (Table III).

Out of 30 patients with menstrual disorders, 25 patients (83.3%) were from the cyclophosphamide therapy group, whereas only five patients without cyclophosphamide therapy (16.7%) had menstrual disorders. Among patients with menstrual disorders in the cyclophosphamide group, 14/25 of them had sustained amenorrhoea, followed by oligomenorrhoea (10/25) and transient amenorrhoea (1/25). In the non-cyclophosphamide group, the majority of them had oligomenorrhoea (3/5), followed by sustained amenorrhoea (2/5), and none of them had transient amenorrhoea. Tables IV and V show the prevalence of menstrual disorders in relation to the phases of cyclophosphamide therapy and the cumulative cyclophosphamide dose, respectively.

In our study, 18 patients had sustained amenorrhoea. 12 patients admitted that they had menopausal symptoms, but only nine patients had hormonal testing as the others refused consent. All nine patients who had hormonal testing were between 35 and 45 years of age, and their hormonal assay confirmed premature menopause. Three patients who had sustained amenorrhoea and had menopausal symptoms, were patients aged more than 45 years, but had no hormonal assay to confirm the menopausal state. Six patients who had sustained amenorrhoea were aged less than 35 years and denied premenopausal symptoms. However, they did not consent to having their hormonal assay performed.

An analysis was made to determine factors that may influence the menstrual disturbances. Logistic regression analysis was employed using complete data for 61 patients in order to study the risk factors for menstrual irregularities. Menstrual irregularity was the dependent variable, and patients' current age, immunosuppressive therapies and cyclophosphamide therapy were found to be the predictive variables ($p < 0.05$) (Table VI). The most significant risk factors in each group were: patients aged more than 40

Table VI. Logistic regression analysis to determine the risk factors for menstrual irregularities.

Independent variables	Wald	degree of freedom	p-value
Current age (years)	3.451	1	0.037
Age at menarche (years)	1.100	1	0.293
Age at diagnosis (years)	2.047	1	0.152
Duration of disease (years)	1.408	1	0.235
SLEDAI score	2.882	1	0.153
Lupus nephritis	6.467	1	0.110
Type of immunosuppressive therapy	8.683	1	0.020
Type of cyclophosphamide regimes	10.451	1	0.015
Haemoglobin	2.965	1	0.850
Serum creatinine	0.241	1	0.621
Proteinuria	0.409	1	0.823
C_3	5.419	1	0.056
C_4	3.566	1	0.059

completed years, patients receiving cyclophosphamide as immunosuppressive therapy, and patients receiving extended induction cyclophosphophamide therapy; with $p < 0.05$ for each group. From the final model analysis, cyclophosphamide therapy alone proved to be an independent risk factor for menstrual irregularities ($p < 0.002$).

DISCUSSION

At present, patients with SLE have a far better prognosis than 40 years ago.[13] The ten-year survival is now estimated to be at 80%–90%.[13] Coinciding with this improved survival, other outcome measures have been scrutinised and they include menstrual disorders. Menstrual disorders such as oligomenorrhoea, transient amenorrhoea and premature menopause are fairly common in these patients.[6] Other menstrual disorders seen in SLE patients included polymenorrhoea and menorrhagia.[14] In our study, 49.2% of SLE patients had menstrual disorders, compared to the 16.7% in the normal healthy population. It shows that SLE patients have a three times higher risk of developing menstrual disorders compared to the normal healthy population. This finding is consistent with previous studies in which the prevalence of menstrual disorders among SLE patients ranged from 15% to 40% .[6,9,10,15,16]

The types of menstrual disorders reported by SLE patients in this study were also consistent with previous studies and they included oligomenorrhoea, transient amenorrhoea and sustained amenorrhoea.[6,9,17] In our study, sustained amenorrhoea was the commonest menstrual disorder observed in this population (53.3%, 16/30); in which 14 were seen in the cyclophosphamide group and two in the non-cyclophosphamide group. This result is consistent with previous studies that have shown sustained amenorrhoea as the commonest menstrual disorder secondary to cyclophosphamide.[15,18,19] A logistic regression analysis was employed using complete data for 61 SLE patients in order to study the risk factors for menstrual disorders in our study population. We found that an abnormal menstrual pattern was the dependent variable, and that patients' age, severity of lupus nephritis and usage of cyclophosphamide therapy including dosage were found to be the predictive variables.

Patient's age is one of the recognised risk factors for menstrual disorders identified in our study. The greater the age, the more likely it is for patients to exhibit menstrual disorders. This finding is consistent with a previous study by Boumpas et al who concluded that the rates of menstrual disorder secondary to ovarian insufficiency became proportionally higher as the age of the patients increased.[9] Other studies also found that patients who were 31 years or older had a higher risk of developing menstrual disorders, in comparison to patients who were less than 30 years of age.[6,14] Another predictor of menstrual disorder that we tested was the SLE disease activity. The patients in our study had premorbidly normal menstrual cycles. Our results show that the inactive phase of SLE had an incremental effect on the risk of developing menstrual disorders compared to the active phase of SLE (Table V). During the active phase, 13/61 patients (21.3%) had menstrual disorders, whereas during the inactive phase, 30/61 patients (49.2%) had menstrual disorders. This result contradicts the traditional idea stemming from uncontrolled observations, that disease activity was a cause of amenorrhoea in women with SLE.[20]

A possible explanation of our findings may lie in the therapy given during the inactive phase. 59% (30/61) of our study population (SLE patients) received cyclophosphamide therapy, a major recognised adverse effect being ovarian toxicity resulting in ovarian insufficiency. 83.3% (25/30) of patients who developed menstrual disorders were from this group. This translates to a five times higher risk compared to those not on cyclophosphamide therapy (83.3% vs. 16.7%).

A comparative study by Medeiros et al showed that the risk of development of ovarian insufficiency in women using intravenous cyclophosphamide was 7.8 times higher compared to non-users.[6] The active phase of SLE included the pre-induction and induction courses of cyclophosphamide, whereas the inactive phase of SLE included the maintenance and post-maintenance courses of cyclophosphamide. The higher risk for menstrual disorders during the inactive phase may just be an expression of the cumulative dose of cyclophosphamide. This is exemplified by the incremental rise in menstrual disorder from the pre-induction to the post-maintenance phases of cyclophosphamide therapy, which is again consistent with other studies (Table IV).[14,16,19,21,22]

The risk of sustained amenorrhoea increased with a higher cumulative dose of cyclophosphamide.[14] Medeiros et al also described that the cumulative dosage of cyclophosphamide plays a major role in determining ovarian toxicity.[6] In that study, SLE patients treated with a cumulative cyclophosphamide dose of greater than 10 g had a 3.2 times higher risk of developing ovarian insufficiency than patients receiving a cumulative dose lower than 10 g.[6] Hormonal testing on the nine patients with sustained amenorrhoea indicated that all of them had premature menopause. There are several limitations to this study. This includes a major reliance on patient recall to ascertain their menstrual histories due to incomplete documentation. Secondly, of the 16 patients with sustained amenorrhoea, only nine consented to having their hormonal assay done. Although the likely cause for the sustained amenorrhoea would still be premature menopause, such postulations could not be confirmed.

In conclusion, we have found that in accordance with previous studies, the prevalence of menstrual disorders among the rural population of Malaysia is three times higher compared to the normal healthy population. We have also found that the commonest disorder is sustained amenorrhoea and that the most important predictors for menstrual disorders are a higher cumulative dose of cyclophosphamide and the age of the patients. This is again in accordance with other studies on menstrual disorders in patients with SLE.

REFERENCES

1. Mills JA. Systemic Lupus Erythematosus. N Eng J Med 1994; 330:1871-9.
2. Lamont DW, Lai MK, Silber SH. Systemic Lupus Erythematosus. In: eMedicine [online]. Available at: www.emedicine.com/emerg/topic564.htm. Accessed January 31, 2007.
3. Buyon JP, Petri MA, Kim MY, et al; SELENA Investigators. Estrogen/cyclic progesterone replacement is associated with an increased rate of mild/moderate but not severe flares in SLE. Ann Intern Med 2005; 142:953-62.
4. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. Int J Fertil 1967; 12(1 pt 2):77-126.
5. Nelson LM, Bakalov V, Pastor C. Amenorrhea. In: eMedicine [online]. Available at: www.emedicine.com/med/topic117.htm. Accessed January 31, 2007.
6. Medeiros MM, Silveira VA, Menezes AP, Carvalho RC. Risk factors for ovarian failure in patients with systemic lupus erythematosus. Braz J Med Biol Res 2001; 34:1561-8.
7. Moncayo-Naveda H, Moncayo R, Benz R, Wolf A, Lauritzen CH. Organ specific antibodies against ovary in patients with systemic lupus erythematosus. Am J Obstet Gynecol 1989; 160(5 pt 1):1227-9.
8. Pasoto SG, Viana VS, Mendonca BB, Yoshinari NH, Bonfa E. Anti-corpus luteum antibody: a novel serological marker for ovarian dysfunction in systemic lupus erythematosus? J Rheumatol 1999; 26:1087-93.
9. Boumpas DT, Austin HA 3rd, Vaughan EM, at al. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Intern Med 1993; 119:366-9.
10. Gonzalez-Crespo MR, Gomez-Reino JJ, Merino R, et al. Menstrual disorders in girls with systemic lupus erythematosus treated with cyclophosphamide. Br J Rheumatol 1995; 34:737-41.
11. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis Rheum 2005; 52:2761-7.
12. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 1992; 35:630-40.
13. Swaak AJG, Nossent JC, Bronsveld W, et al. Systemic lupus erythematosus outcome and survival; Dutch experience with 10 patients studied prospectively. Ann Rheum Dis 1989; 48:447-54.
14. Ioannidis JPA, Katsifis GE, Tzioufas AG, Moutsopoulos HM. Predictors of sustained amenorrhea from pulsed intravenous cyclophosphamide in premenopausal women with systemic lupus erythematosus. J.Rheumatol 2002; 29:2129-35.
15. Ioannidis JP, Boki KA, Katsorida ME, et al. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. Kidney Int 2000; 57:258-64.
16. Park MC, Park YB, Jung SY, Chung IH, Choi KH, Lee SK. Risk of ovarian failure and pregnancy outcome in patients with lupus nephritis treated with intravenous cyclophosphamide pulse therapy. Lupus 2004; 13:569-74.
17. Dhabhai R, Kalla G, Singhi MK, Ghiya BC, Kachhawa D. Dexamethasone-cyclophosphamide pulse therapy in systemic lupus erythematosus. Indian J Dermatol Venereol Leprol 2005; 71:9-13.
18. Lower EE, Blau R, Gazder P, Tummala R. The risk of premature menopause induced by chemotherapy for early breast cancer. J Womens Health Gend Based Med 1999; 8:949-54.
19. Wang CL, Wang F, Bosco JJ. Ovarian failure in oral cyclophosphamide treatment for systemic lupus erythematosus. Lupus 1995; 4:11-14.
20. Lim GS, Petri M, Goldman D. Menstruation and systemic lupus erythematosus: a case-control study. Arthritis Rheum 1993; 36 (5 suppl):R23.
21. Liu G, Chen Y, Wang L, et al. [The risk of sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy.] Hua Xi Yi Ke Da Xue Xue Bao 2001; 32:294-5. Chinese.
22. Katsifis GE, Tzioufas AG. Ovarian failure in systemic lupus erythematosus patients treated with pulsed intravenous cyclophosphamide. Lupus 2004; 13:673-8.