

# Ovarian Functions and Reproductive Preservation in Patients with Systemic Lupus Erythematosus: A Review of Literature

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## Abstract

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease of unknown etiology. The course of SLE is highly variable, with recurrent remission and exacerbation. The prevalence of the disease is affected by race, age and gender. In this review of literature, we tried to surf the web searching for all of articles concerned with ovarian functions, reserve and preservation among patients with SLE.

**Keywords:** Systemic lupus; Ovarian function; Ovarian reserve; Fertility preservation

## Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease of unknown etiology. The course of SLE is highly variable, with recurrent remission and exacerbation. The prevalence of the disease is affected by race, age and gender. It ranges from approximately 40 cases per 100,000 persons in North Europe, to more than 200 per 100,000 of the black population in the United States and the United Kingdom. SLE affects females more than males, with a female-to-male ratio of 9:1 and the peak onset of the disease is during the childbearing period [1,2].

The life expectancy of SLE patients has improved too much in last decade. The four years survival rate was fifty per cent in 1950s however, the fifteen years survival rate is about eighty percent recently [3]. As the females in the child bearing period are the most affected group, a lot of studies highlighted the effect of the disease on the gonadal function. The gonadal function of patients with SLE can be altered by many factors which may be related to pathology of the disease or may be related to treatment. The pathology of SLE may cause physiologic anovulation, hypothalamic-pituitary-ovarian axis dysfunction or thyroid disorders. Meanwhile, treatment with high doses of corticosteroids, cyclophosphamide and immunosuppressive drugs may alter ovarian function [4].

Li et al. [5] and Faustman et al. [6] found association between autoimmune disorders like SLE, diabetes, rheumatoid arthritis and the presence of auto antibodies against the ovaries. This was confirmed by Luborsky [7] who suggested that 69% of the etiology of premature ovarian failure among her study group is autoimmune based.

Evaluation of ovarian function is extremely complex. It is usually based on clinical parameters which proof ovulation, and laboratory evidence of ovulation as mid-luteal serum progesterone. In addition, parameters of ovarian reserve like follicular stimulating hormone (FSH), luteinizing hormone (LH), anti-mullerian hormone (AMH) and inhibin are usually used [4].

## Effect of SLE on Menstrual History

A lot of case control studies have been published to explain the effect of SLE on ovarian function on adolescents and young women.

In the study of Silva et al. [4], twenty three female patients with SLE were followed for one year. Their age range was between 16 years and 9 months to 22 years and 10 months. All patients had menarche before and all of them were nonusers of contraceptives. Patients with amenorrhea and those with unplanned pregnancy were excluded.

Disease activity was measured by systemic lupus erythematosus index (SLEDAI). They found the mean age of menarche of patients with SLE was significantly higher when compared with the mean age of menarche of 2578 normal Brazilian adolescents girls ( $13.5 \pm 1.4$  years versus  $12.5 \pm 1.3$  years respectively,  $p=0.0002$ ).

The same results were obtained by Medeiros et al. [8] who found the mean age of menarche significantly higher in patients of SLE versus the control group ( $13.3 \pm 1.4$  years versus  $11.56 \pm 1.5$  years,  $p=0.0008$ ) despite the similarity in maternal age of menarche in both groups. Patients participated in both studies had normal secondary sexual characteristics according to Marshall and Tanner's pubertal changes.

Aikawa et al. [9] found that the mean age of menarche significantly higher in patients of SLE versus the control group as they compared 27 SLE patients with 13 healthy adolescent Brazilian girls ( $p=0.03$ ). In contrast to the previous two studies SLE group had significantly lower frequency of Tanner pattern versus controls. ( $p=0.068$ ).

The effect of SLE on cycle regularity was variable. Silva et al. [4] found no statistical correlation between patients of SLE and the control group regarding the mean phase length of menstrual cycle. This was confirmed by Shabanova et al. [10] who found the mean length of menstrual cycle and the mean amount of menstruating blood were similar in patients with SLE and age matched controls. However, number of cases with oligomenorrhea (cycle>35 days) was significantly higher in the group of SLE.

On the other side, number of cases with menstrual irregularity (presence of long cycle>36 days or short cycle<24 days) and the mean duration of menstrual blood flow were significantly higher in SLE group than the control group ( $p=0.0009$ ,  $p=0.0047$  respectively) [8].

Disease duration and disease activity score was significantly correlated and delayed age of menarche menstrual disorders in most studies [10,11].

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Silva et al. [4] found patients with age of menarche more than 13.5 years experienced disease duration over 6 years and 7 months before the first menstruation. This may be either a reflection of severity or related to large dose of immunosuppressive administration.

### Effect of SLE on Ovarian Reserve

Subclinical affection of ovarian reserve tests were observed in patients of SLE. Serum FSH and/or LH were significantly higher in some studies [8,12] and significantly lower in others versus controls although they remain within reference value [13].

Lower median antral follicle count (AFC) was significantly observed by pelvic ultrasound scan in SLE patient when compared with the controls [9,12].

Furthermore, midcycle serum progesterone was significantly lower in SLE patients versus controls. It was also significantly lower in group of patients with SLEDAI score  $\geq 11$  than patients with score  $<11$  which may explain impaired ovulation and cycle irregularity in those patients [10].

AMH is a good predictor of ovarian reserve which is significantly lower in SLE patients when compared with age matched group [14].

Araujo et al. [11] detected anti-corpus luteum antibodies (anti-CoL) only in sera of some SLE patients and they did not detect them in any of the controls (the antigen was prepared from cell extract of bovine corpus luteum). Interestingly, they found both AFC and median AMH level were lower in lupus patients with positive anti-CoL versus those who are negative although the difference was not statistically significant.

After correlation of all parameters of ovarian reserve tests to each other's, Ulug et al. [12] found that age of the patient had strong positive association with FSH ( $r=0.83$ ,  $p=0.039$ ). Moreover, their multivariate analysis showed that AFC was the only significant predictor of menstrual irregularity (1.321, 95% CI 1.014–1.372;  $P=0.03$ ) in SLE patients.

### Effect of SLE Treatment on Ovarian Function

#### Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are indicated in treatment of pain and inflammation in autoimmune diseases. They inhibit prostaglandin synthesis via inhibition of cyclo-oxygenase (COX) enzyme. Low concentration of the pre-ovulatory follicle may prevent ovulation [15,16].

A prospective randomized trial revealed that five women out of twelve treated with ibuprofen experienced delayed ovulation and follicle rupture [15]. Furthermore, Delayed ovulation and low serum progesterone was observed in 20 women treated with meloxicam for four cycles [17]. NSAIDs may be a cause of reversible anovulation but still large sample size study is needed.

**Glucocorticoids:** Hydrocortisone administration was found that it alters pituitary ovarian axis by reducing LH pulse frequency and concentration [18]. Therefore menstrual cycle irregularity may be a result of corticosteroids intake in SLE patients [19]. In contrast, a small size study of juvenile onset SLE revealed that menstrual cycle irregularity was not different in patients on daily low dose (10 mg) or high dose ( $>20$  mg) of prednisone [20].

Most studies reported that there was no statistical difference in cumulative dose of prednisolone between SLE patient with normal and abnormal ovarian function [4,8,21]. They postulated that low dose of steroids used by SLE patients (10-20 mg/day) may not affect pituitary gonadotrophins release and not significantly alter the ovarian function [22].

### Immunosuppressive drugs

**Azathioprine:** The mean dose of azathioprine was similar among SLE patients with normal and abnormal ovarian function [4,23]. It does not impair female fertility and should be used as alternative to other immunosuppressive as much as possible. It is used as adjuvant or alternative to cyclophosphamide in treatment of lupus nephritis without affection of productive function [24,25]. Moreover, there was no proof that azathioprine increase the incidence of premature ovarian failure (POF) in SLE patients [22].

**Cyclophosphamide:** Cyclophosphamide is still the golden treatment of severe SLE because of low cost and good patient compliance. However it impairs gonadal function in both sex and the risk usually related to the cumulative dose and age. It destructs primordial follicle therefore cause follicle depletion and POF [23].

Stromal fibrosis, reduced number of follicles and retarded follicular development are characteristic in histological examination of ovaries after CYC therapy [26].

An American retrospective study reported that ovarian reserve was significantly reduced in SLE patients treated intravenous cyclophosphamide (IV CYC) versus those without this treatment [14]. This was confirmed by another prospective Brazilian study that ovarian reserve was significantly reduced in SLE patients treated IV CYC when compared with age matched controls [8]. This explains the subclinical effect of CYC on young age patients as many studies revealed normal pubertal development and onset of menses in young female patients treated with CYC as a single agent during childhood [27].

The risk of POF in SLE patients treated with CYC varies from 15% to 60% depending on the age [1,2]. There is no safe dose of CYC and the risk of POF is higher with oral CYC than with pulses of CYC [8].

Patients with renal lupus or with severe cutaneous manifestation depending on daily oral dose of CYC can have amenorrhea within a year. Moreover 70% of them may develop POF. IV CYC can induce amenorrhea in 45% of patients depending on the cumulative dose and dose timing in relation to menstrual cycle. It was found that less side effect if it is administrated during menses [28].

A prospective randomized study was done by Manger et al. [29] on 63 premenopausal SLE patients. They measured FH and LH before, during and after CYC therapy. Their results revealed that 60% of the patients developed POF diagnosed by the presence of amenorrhea and high serum FSH  $>40$  mIU/mL. Age was a very determinant factor as 39% of patients were below 30 years while, 59% were between 30 and 40 years.

In the study of Marder et al. [30] 48 pre-menopausal lupus patients were classified into three treatment groups: first one was treated with CYC alone, the second was treated with CYC and GnRH $\alpha$  while the third did not receive any treatment. They found median AMH was significantly lower in the first group versus the second and also between the first group and the third one ( $p=0.015$ ,  $p=0.018$ , respectively).

Unfortunately, most of large studies done about the effect of CYC about the incidence of POF were retrospective as prospective studies will need a long time and will be costly. They reported that IV CYC increases the incidence of POF significantly among the patients aged from thirteen to twenty years compared with cohort treated before the age of twelve [31]. Estimated risk of sustained amenorrhea or POF in those below 25 years is very low (0-11%) [1,11].

Brunner et al. [32] found alteration in ovarian reserve parameters

in SLE patients treated with cyclophosphamide versus those not treated as median FSH was significantly higher in CYC group compared to patients without CYC however lower median AFC and AMH were observed in CYC group ( $p=0.032$ ,  $p=0.004$ ,  $p=0.001$ , respectively).

In the study of Mok et al. [33] the mean AMH in patients with SLE after age adjustment was significantly lower in patients received CYC compared to those who were not users ( $p=0.04$ ). The median time between last dose of CYC and AMH assay was 6.7 years (IQR 3.4-88.5). Linear regression analyses revealed that age and cumulative dose of CYC were independently responsible for AMH decline. Neither the route of CYC administration nor the treatment interval was associated significantly with drop of ALH. By using ROC curve with AUC of 0.88, undetectable level of AMH was at cumulative dose of CYC 5.9 g (sensitivity 0.75 and specificity 0.8) when age was fixed at 30 years.

**Methotrexate:** Methotrexate (MTX) acts on rapidly dividing cells which include ovary and endometrial cells there for it may hinder the fertility especially in those with already low ovarian reserve [34]. However animal studies found no statistically significant changes in AMH level pre and after treatment of methotrexate even after repeated injection [35].

In the study of Silva et al. [4] there was no difference in frequency and the mean dose of methotrexate in both groups of normal and abnormal menstruation. Moreover there was no statistical correlation between the age of menarche and the duration of methotrexate used before first menstruation.

Silva et al. [4] found that the percentage of patients received methotrexate in the group of SLE patient with low FSH or LH and those in the group of normal FSH or LH were similar.

Medeiros et al. [8] found no significant difference between methotrexate users in SLE patients with normal and abnormal menstrual cycle.

Brunner et al. [32] studied for the first time that high cumulative dose of methotrexate in treatment of juvenile SLE may impair ovarian function. They found negative correlation between cumulative dose of methotrexate and AMH level in SLE patients treated with methotrexate and never used CYC ( $p=0.027$ ,  $r=-0.507$ ).

**Mycophenolate mofetil:** Mycophenolate mofetil is a drug used mainly in treatment of lupus nephritis as alternative to CYC with less toxicity. Some new trials focus its role in role in remission maintenance like azathioprine [36].

Silva et al. [4] found no significant difference in number of patients receiving mycophenolate mofetil in the group of SLE patient with low FSH or LH and those in the group of normal FSH or LH.

Medeiros et al. [8] found no significant difference in number of patients receiving mycophenolate mofetil in the of SLE patients with normal and abnormal menstrual cycle.

In the study of Mok et al. [33] the mean AMH level in mycophenolate mofetil users versus non-users was insignificant. It was used in many studies as an alternative to other immunosuppressive agents even in treatment of non-renal lupus due to its low profile toxicity [37]. It was not proved to impair the female fertility.

Brunner et al. [32] found no correlation between AMH level, AFC and cumulative dose of mycophenolate mofetil [1,14].

## Ovarian Function Preservation in Young SLE Patients

### Gonadotropin releasing hormone analogue (GnRH-a)

The idea of continuous Gn-RH-a administration in SLE patients

treated with CYC is to induce a state of temporary medical castration. Gn-RH-a suppress the ovulation and reduce oestrogen and progesterone production to the prepubertal level. Furthermore, it decreases the ovarian blood supply and hence decreases the circulating level of CYC reaching the ovaries [38].

Blumenfeld et al. [38] had 3 studies that confirmed reduced ovarian injury in patients received Gn-RH-a during chemotherapy treatment. However, the study group included SLE patients and cancer patients.

In the study of Somers et al. [39], they compared 20 female SLE patients (age<35 years) who received regular monthly doses of IV CYC and monthly dose of parenteral Gn-RH-a versus age matched controls. Controls were randomly selected from female SLE patients in the Michigan Lupus Cohort who received IV CYC before but did not receive Gn-RH-a. Each patient received Gn-RH-a was randomly matched with one control within  $\pm 5$  years of age and  $\pm$  cumulative gram of CYC. After follow up for a minimal 3 years POF was significantly lower in the group received Gn-RH-a versus who did not. The cumulative preservation of ovarian function in the Gn-RH-a treated group was significantly higher than the control group ( $p=0.04$ ). Analysis of Cox regression revealed that the incidence of POF within 10 years of CYC therapy in the study group is less than one tenth of controls (hazard ratio 0.09, 95% confidence interval 0.01–0.8).

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