

## Can pregnancy induce relapse in systemic lupus erythematosus (SLE)?

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which mostly affects women of reproductive age. We evaluated the impact of pregnancy on maternal/fetal health, the pattern of organ involvements and the flare-up risk. In a retrospective study we studied the thirty-year medical records of patients between 1976-2005. Maternal, neonatal and infantile health data was retrieved. Incidence of flare-ups, pattern of organ involvements and the outcome of pregnancy was analyzed. We studied 155 pregnancies in 129 SLE patients. Mean age of patients was  $27.0 \pm 5.5$  years (range, 16-44). Thirty one cases (20.2%) experienced flares in the course of pregnancy. During pregnancy, SLE disease activity index (SLEDAI) score increased in 92 (59.3%) patients (median increase = 6 scores). On the other hand, 38 cases (24.5%) SLEDAI score remained unaltered and in 25 cases (16.1%) SLEDAI score decreased (median decrease = 1). Mean SLEDAI during pregnancy were significantly higher than preconceptional scores (P-value = 0.002). Term delivery was more common in quiescent SLE (54.2% vs. 34.6%, P-value = 0.04). Number of therapeutic abortions was higher in active SLE (38.5% vs. 10.2% P-value = 0.003). In this study increased SLEDAI and flare-up episodes were observed during pregnancy. However the majority of cases did not face major fetal or maternal complications.

**Keywords:** pregnancy, SLE disease activity index (SLEDAI) score, systemic lupus erythematosus (SLE).

### Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease mostly affecting women of reproductive age. SLE studies in Iran have reported the median age of disease is 24.5 years and female to male ratio of 8.8/1 [1]. The complex interrelation between SLE and pregnancy has been the subject of an ongoing dispute. This is partly due to the underlying role of sex hormones and prolactin [2]. Understanding the impact of SLE on maternal or neonatal outcome is substantial to provide optimized care during pregnancy and puerperium [3].

Pregnancy in SLE cases may result in maternal or fetal complications [4]. In lupus pregnancies there is an increased risk of maternal morbidities such as cesarean sections, preterm labor and preeclampsia [5]. Fetal morbidity and mortality such as intrauterine growth restriction (IUGR), premature birth, stillbirth and neonatal deaths has been indicated in lupus pregnancies [6]. The stable disease activity prior to conception is the key predictor of pregnancy outcome [7]. Literature has reported varying rates of lupus flare up during pregnancy and puerperium [8]. Signs and

symptoms such as arthritis, skin rash, proteinuria, thrombocytopenia, leucopenia and anti-ds-DNA expression are among the key clinical findings which must be examined in SLE pregnancies. The lupus flares occasionally mimic clinical picture of preeclampsia and commonly coexist with it [9]. Hence SLE flare-up during pregnancy, count as diagnostic and therapeutic challenge. Pregnant SLE cases should be intricately managed by a collaborative team.

During recent decades, improvements in maternal management have led to dramatic dip in pregnancy loss [10]. Thus it is assumed that if disease is thoroughly controlled, there will be a favorable maternal and fetal outcome [11]. The improved pregnancy outcome has led the patients to more frequently consider pregnancy [4].

There has not been a comprehensive study in Iranian SLE patients during the pregnancy period. Therefore we designed a study based on the 30-year record in our referral center. In this study we aimed to elucidate the pattern of organ involvements in pregnancy and the severity of SLE flare ups in this critical period.

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## Materials and Methods

In our retrospective study, we investigated the pregnancies in SLE population. Lupus patients had referred to SLE clinic of Shariati hospital at Tehran University of Medical Sciences (TUMS) which is a nationwide academic referral center for rheumatologic disorders. Maternal, neonatal and infantile health data was retrieved from our database and patient's files. Incidence of flare ups, pattern of organ involvements and the outcome of pregnancy was analyzed. Furthermore number of spontaneous or therapeutic abortions were registered.

### Statistical Analysis

In order to assess the relation between SLEDAI before and during pregnancy, Spearman correlation test was applied. We investigated the correlation between organ involvements before and during pregnancy via McNemar test. To unravel the correlation between qualitative parameters Chi-square test was used. In categories with limited sample size we applied Fischer test and Odds Ratio (OR), and 95% confidence intervals (95% CI) were calculated. Due to non-normal distribution of patients' scores, non-parametric test Mann-Witney U test was used to compare scores between groups. In order to determine the independent predictive factors, logistic regression was applied. P-value = 0.05 was set as significant. Collected data was analyzed via SPSS software version 22.0 (Chicago, IL).

### Ethical approval

The study proposal was discussed and approved by the ethical committee of TUMS. The study was conducted in accordance with the Declaration of Helsinki. A code is assigned to each of the SLE patients. The researchers excerpted data from the coded database without revealing the identity of the patients.

## Results

We studied 155 pregnancies in 129 SLE patients. Mean age of patients was  $27.0 \pm 5.5$  years (range, 16-44).

### Maternal outcome of pregnancy

Pregnancy in 2 cases (1.3%) occurred in the active phase of disease. In the remaining 153 cases (98.7%), pregnancy occurred in the quiescent phase of SLE. Of these quiescent SLE cases, 31 cases (20.2%) experienced flare up in the course of pregnancy. Flare ups had become under control in 2 out of 31 cases (6.5%). In comparison with pre-conception period, during pregnancy the SLEDAI score decreased in 25 cases (16.1%) with median decrease of 1 score.

Meanwhile in 92 patients (59.3%) SLEDAI score increased (median: 6 scores) and in 38 pregnancies (24.5%) SLE activity score remained unaltered. Overall SLEDAI scores significantly increased in comparison with pre-conception period (P value= 0.002).

Among patients with active SLE, central nervous system (CNS) vasculitis in 19.3%, worsening of proteinuria in 29%, thrombocytopenia in 8.4%, leucopenia in 10.3%, Skin rash in 58.1%, skin ulcer in 19.3%, and arthritis in 7.7% were seen.

Of laboratory data, anti-ds-DNA expression was associated with SLE activity. In flare-up cases 45.2% had positive anti ds-DNA while in quiescent cases 16.1% had positive anti ds-DNA (P value= 0.0012). Hypocomplementemia was detected in 38.7% of active lupus cases which was significantly more common in comparison with quiescent subset (11.3%, P-value= 0.0008).

### Infantile outcome of pregnancy

Only two pregnancies (1.3%) occurred during the active phase of SLE. In one case, SLE was controlled during pregnancy however the pregnancy led to spontaneous abortion. Pregnancy in the other active lupus case ended in term delivery.

Overall among 155 pregnancies, term pregnancy occurred in 73 cases (47%), 7 cases of preterm labor (4.5%), spontaneous abortion and therapeutic abortion in 30 (19.4%) and 22 (14.2%) patients respectively. Stillbirth occurred in 13 cases (8.4%). Among patients with quiescent lupus during pregnancy, term infant in 54.2%, preterm delivery in 5.1%, stillbirth in 9.3%, spontaneous abortion in 21.2% and therapeutic abortion in 10.2% of them were executed.

In active lupus SLE (Flare-ups), term delivery in 34.6%, preterm delivery in 3.8%, stillbirth in 7.7%, spontaneous abortion in 15.4% and therapeutic abortion in 38.5% of them were observed. Preterm birth, spontaneous abortion and stillbirth were more common in non-active SLE subset; however the difference with active SLE was statistically insignificant. Detailed description of infantile outcomes of pregnancies is tabulated in Table 1.

### Renal involvement and maternal/infantile outcome

We had data of renal biopsy of 46 patients. All the patients of this group had inactive SLE at conception. According to our data, even though a linear correlation between renal involvement and unsuccessful pregnancy (stillbirth or abortion) was seen however no significant correlation was detected (P = 0.057).

**Table 1.** Pregnancy outcome: comparison between active and quiescent systemic lupus erythematosus

Pregnancy outcome	Flare-ups	Quiescent	Total	P-value
	N (%)	N (%)	N (%)	
Term infant	9 (34.6)	64 (54.2)	73 (50.7)	0.04
Preterm infant	1 (3.8)	6 (5.1)	7 (4.9)	0.55
Stillbirth	2 (7.7)	11 (9.3)	13 (9.0)	0.23
Spontaneous Abortion	4 (15.4)	25 (21.2)	29 (20.1)	0.667
Therapeutic Abortion	10 (38.5)	12 (10.2)	22 (15.3)	0.003
Total	26	118	144	

Table 2 demonstrates the distribution of various levels of renal involvement during pregnancy between flare-up and quiescent subsets.

## Discussion

Our results revealed the SLEDAI scores during pregnancy increased significantly. In 59% of patients SLEDAI score increased and 20.2% of patients experienced flare-up episodes during pregnancy. The surging SLEDAI pattern in pregnancy was comparable with numerous previous studies and reported figures [3, 12]. However, a number of case-control studies have denied any significant increase in SLE activity during pregnancy in comparison with non-pregnant SLE patients [13-16]. Furthermore, past reports have suggested contrasting results regarding incidence of SLE flares during pregnancy [17]. The prevalence rate of flare in our study was within reported prevalence brackets. This clinical difference in various reports may be partly due to the inclusion criteria applied in different studies. In addition, the varying methods of defining SLE activity and flares in SLE pregnancy, impedes a resolute conclusion.

Our major findings in active SLE during pregnancy included CNS vasculitis, arthritis, skin rash, ulcer, leucopenia, thrombocytopenia and escalated proteinuria. Musculoskeletal symptoms are common among pregnant SLE patients. Low back pain, effusions and worsened fibromyalgia are most notable reported comorbidities [18]. In our study in 7.7% of SLE pregnant cases arthritis was detected.

Thrombocytopenia was detected in 8.4% of our

studied patients. In 8% of normal pregnancies mild thrombocytopenia may develop with no clinical significance [19]. Furthermore In our study, 16.8% of cases had hypocomplementemia while in 29% of pregnancies deteriorated proteinuria was detected. Lower complement levels indicate serum consumption due to underlying inflammatory process. The association of hypocomplementemia during pregnancy with SLE activity or fetal outcome must be interpreted cautiously. The concordance of low complement levels with high SLE activity is predictive indicate poorer fetal and maternal outcomes in SLE [20-22]. Likewise proteinuria is another biochemical factor associated with poor pregnancy outcome in SLE [23].

Various clinical and paraclinical factors have predictive value in the forthcoming SLE activity during pregnancy. The history of highly-active preconceptional disease and discontinuation of antimalarial therapy prior to conception were heeded as two main predictive factors for flare during pregnancy [24, 25]. Moreover, preexisting proteinuria and anti-ds-DNA expression are frequently associated with SLE flares during pregnancy and implicated in poor prognosis of pregnancy [26]. Accordingly our results unraveled anti ds-DNA expression before pregnancy corresponds to increased SLE activity during pregnancy. On the other hand, in lupus flares during pregnancy, anti- ds-DNA positivity was significantly more common than stable lupus. Yang et al. [27] reported a similar difference between active and stable SLE subsets. Study by Clowse et al. [22] has revealed the association of anti- ds-DNA expression and highly-

**Table 2.** The distribution of various levels of renal involvement during pregnancy between flare-up and quiescent subsets of systemic lupus erythematosus

Renal involvement	Flare-up (n=6) N(%)	Quiescent (n=40) N (%)	Total (n=46) N (%)
I	0	1 (2.5%)	1 (2.2%)
II	1 (16.7%)	7 (17.5%)	8 (17.4%)
III	2 (33.3%)	18 (45%)	20 (43.5%)
IV	3 (50%)	11 (27.5%)	14 (30.4%)
V	0	3 (7.5%)	3 (6.5%)

active SLE led to dramatic increase of perinatal mortality as well as decrease in full-term births.

Of signs of active SLE, leucopenia was implicated in poor pregnancy outcome in our studied cohort via multivariate analysis. No significant association between other clinical findings and fetal wastage was detected. Previous studies have introduced other predictive factors for fetal loss such as preconceptional active lupus nephritis, history of fetal loss, and high antiphospholipid antibody titers [30-36].

According to our results term delivery was significantly more common among quiescent subset. Meanwhile we detected a higher rate of spontaneous abortion amongst non-active subset which was statistically insignificant. It is noteworthy that a significantly-higher rate of therapeutic abortions was executed in active SLE patients. This notion may partly contribute to the lower rate of term birth in active lupus cases. A number of previous studies have suggested the significant association between SLE activity and preterm delivery [37, 38]. Study by Yang et al. has revealed that preconceptional SLE activity as the pivotal predictive factor for preterm delivery [38].

Interestingly we detected no significant association

between renal involvements and pregnancy outcome. This finding was in contrast with previous studies [39, 40]. The degree of renal functioning at the time of conception is the key factor predicting fetal and maternal prognosis [41]. A study by Stojan et al. [4] has introduced active lupus nephritis at the time of conception, as the major predictor of preeclampsia in SLE. This discordance between our study and literature might be partly due to non-active status of SLE prior to pregnancy, or due to the limited number of available renal biopsies.

In this study increased SLEDAI and flare-up episodes were observed during pregnancy. However the majority of cases did not face major fetal or maternal complications. We suggest that intricate preconceptional control of SLE improves the maternal/fetal outcome and limits the disease manifestations during pregnancy. Large-scale prospective studies are warranted to address the influence of various predicting factors in maternal and fetal prognosis.

### Conflict of interests

Authors have no conflict of interests.

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