# The Role of Lupus Nephritis in Development of Adverse Maternal and Fetal Outcomes During Pregnancy

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Original Article

## ABSTRACT

**Background:** We aimed to investigate the relationship of lupus nephritis (LN) with fetal and maternal outcomes of pregnant patients with systemic lupus erythematosus (SLE).

**Methods:** In a retrospective study, profiles of pregnant women with SLE were selected. Before pregnancy and at the end of first, second and third trimesters, SLE disease activity index-2K was assessed. Clinical and laboratory evaluations were carried out regularly. Maternal and fetal outcomes were recorded. Assessments of the crude effects of statistically significant variables on pregnancy outcomes were performed through multivariate regression analysis.

**Results:** 72 pregnancies in 65 patients were recorded. The mean age of LN patients was 28.7 years, whereas the mean age of patients with clinical nephritis was 26.1 years. No woman with LN experienced pre-term labor or stillbirth. 16 pregnancies either ended in abortion or experienced preeclampsia of which seven had LN. Multivariate logistic regression analyses showed that LN and positive antinuclear antibody were related to preeclampsia, whereas age of SLE development was associated with pre-term labor. Combined maternal and fetal outcomes were associated with the past history of abortion and LN. LN was associated with preeclampsia and SLE flare.

**Conclusions:** Absence of LN was in favor of prevention of SLE flare and preeclampsia.

**Keywords:** Iran, lupus nephritis, outcome, pregnancy, systemic lupus erythematosus

## INTRODUCTION

The behavior of systemic lupus erythematosus (SLE) in pregnant women has been seriously investigated too tight in the past 50 years.[1] The rate of flare of SLE during pregnancy period in various studies has been different, from about 15% to around 50%.[2-6] It has been even higher when the kidneys were actively involved.[2,7] Although SLE mainly targets the women of reproductive age, its behavior during

pregnancy has not been definitely conclusive. However, generally speaking, the rates of adverse fetal outcomes such as miscarriage, stillbirth, neonatal lupus syndrome, intrauterine growth retardation (IUGR), pre-term labor and low birth weight, and the rates of adverse maternal outcomes such as hypertension, preeclampsia and eclampsia have been increased.[8-10] Some of the related risk factors such as anti-double stranded DNA (anti-ds DNA) antibody and hypocomplementemia have been recognized[5,8,11-13] and some remained to be definitely addressed. The impacts of SLE on mother and fetus have been investigated in several parts of the world,[3,5,14-17] but given the scarcity of such long-term investigations in Iran, the current study was carried out to further assess the fetal and maternal outcomes of this group of patients. The clarity of such relationship will illuminate the preventive measures that could be applied to protect mother and fetus in pregnant women with SLE.

## METHODS

This was a retrospective cohort study. Profiles of all women diagnosed with SLE according to the American College of Rheumatology criteria[18] between 1998 and 2012 in lupus clinic were reviewed. Those who experienced pregnancy were enrolled. The study protocol was approved by the University Ethics Committee. The patients were contacted by phone calls to obtain their oral informed consents and missing information of profiles. Demographic, past history, clinical, serological and therapeutic data related to the time between SLE diagnosis and pregnancy outcome was gathered. Exclusion criteria included diagnosed with SLE during the pregnancy period, elective abortion and moving out of the covered area before pregnancy termination. SLE activity in each patient was assessed using systemic lupus erythematosus disease activity index-2K (SLEDAI-2K),[19] before pregnancy and at the end of first, second and third trimester to monitor the SLE activity. Laboratory assessments included antinuclear antibody (ANA), anti-ds DNA antibody, anti-cardiolipin, IgM and IgG, anti-β2 glycoprotein I IgM and IgG, anti-SSA Ab, anti-SSB Ab, C3 and C4. Laboratory evaluations were executed according to the standard routine techniques. Clinical nephritis was considered if they had any of the following criteria during the period of hospital admission: 24-h proteinuria >0.5 g/day or urinary red blood cell casts. Past history of lupus nephritis (LN) was recorded too. Renal biopsies were studied by hospital pathologists and categorized according to the 2004 classification of International Society of Nephrology/Renal pathology Society (ISN/RPS)[20] as follows: Class I – minimal mesangial LN; Class II – mesangial proliferative LN; Class III – focal LN; Class IV – diffuse LN; Class V – membranous LN; and class VI – advanced sclerosing LN.

### Outcomes

Maternal outcomes included no complication, SLE flare up, preeclampsia and eclampsia. Fetal outcomes included no complication, stillbirth, abortion, IUGR and pre-term labor.

#### *Definitions of outcomes*

Stillbirth was defined as intrauterine fetal death after 24$^{th}$ week of pregnancy. Abortion was considered as fetal loss before 24$^{th}$ of pregnancy. IUGR was considered when fetal growth didn't meet it potential of maximum growth. Pre-term labor was set as delivery before 37$^{th}$ week of pregnancy. Neonatal death was defined as the death of live infant in the first 28 days after delivery. Preeclampsia was defined differently according to the presence or absence of baseline hypertension and the amount of proteinuria. New onset of hypertension and proteinuria >300 mg/day after 20$^{th}$ week of pregnancy was considered preeclampsia in those with proteinuria <300 mg/day and no hypertension at baseline. New onset of hypertension and doubling 24-h urinary proteins or urine/creatinine ratio after 20$^{th}$ week of pregnancy was considered superimposed preeclampsia in those with proteinuria >300 mg/day and no hypertension at baseline. 30 mmHg or higher increase in systolic blood pressure and 15 mmHg or higher increase in diastolic blood pressure over the baseline values and doubling proteinuria was defined as superimposed preeclampsia in those with hypertension and proteinuria >300 mg/day. Ecclampsia was defined as the occurrence of tonic-clonic seizures in pregnant women with preeclampsia. SLE flare was considered when SLEDAI increased >3.[21]

### Statistical analysis

Student *t*-test and Mann-Whitney U test were applied to analyze parametric and non-parametric continuous variables, respectively. Univariate analysis was used to evaluate single variable effects on adverse fetal and maternal outcomes. Those with

$P < 0.05$ were considered significant and entered into logistic regression analysis. Multivariate regression analysis was applied to assess the crude effects of statistically significant variables of univariate analysis on pregnancy outcomes. The odds ratios and the 95% confidence intervals (CIs) were calculated in the regression analysis. Potential variables related to the adverse maternal and fetal outcomes included the number of previous pregnancies before and after SLE diagnosis, past history of maternal and fetal outcomes, age of current pregnancy, age of SLE diagnosis, SLEDAI score, serologic evaluations and administered medications since 6 months before pregnancy to the end of pregnancy including prednisolone, hydroxychloroquine, azathioprine and cyclosporin A. Software Package for Social Sciences 17 (SPSS, Chicago, IL) was used for data analyses.

## RESULTS

72 pregnancies, in 65 patients were included in the final analysis. The baseline features and the clinical characteristics are summarized in Table 1.

**Table 1:** Baseline demographic, clinical, laboratory and therapeutic characteristics of patients

| Baseline characteristics | Total | Non-nephritis | Nephritis | | *P* value |
|---|---|---|---|---|---|
| | | | Clinical | Biopsy proven | |
| Number of pregnancies | *n*=72 | *n*=58 | *n*=9 | *n*=5 | 0.37 |
| 1 | 65 | 52 | 8 | 5 | 0.42 |
| 2 | 5 | 5 | 0 | 0 | |
| 3 | 2 | 1 | 1 | 0 | |
| Mean age (range) | | | | | |
| 1st pregnancy (years) | 28.2 (19-41) | 28.7 (19-41) | 26.1 (20-32) | 25.4 (20-33) | 0.11 |
| 2nd pregnancy (years) | 28.85 (23-36) | 28 (23-36) | 34 | - | 0.26 |
| 3rd pregnancy (years) | 31 (25-37) | 25 | 37 | - | - |
| Mean age (years) of SLE diagnosis (range) | 22 (12-34) | 22.6 (15-34) | 20.9 (12-32) | 18 (15-24) | 0.11 |
| Mean SLEDAI score (SD) | | | | | |
| Before pregnancy | 1.3 (1.6) | 1.1 (1.2) | 1.4 (0.89) | 3 (3.4) | 0.04 |
| 1st trimester | 1.8 (1.86) | 1.2 (1.3) | 3.8 (0.98) | 6.75 (2.9) | 0.0001 |
| 2nd trimester | 1.95 (1.86) | 1.4 (1.6) | 3.2 (1.1) | 5.25 (0.96) | 0.0001 |
| 3rd trimester | 2.1 (2) | 1.34 (1.9) | 3.5 (1.4) | 7.5 (0.7) | 0.01 |
| Serology ever, *n* (%) | | | | | |
| ANA | 62 | 51 | 7 | 4 | 0.18 |
| Anti-ds DNA Ab | 56 | 46 | 6 | 4 | 0.96 |
| Anti-cardiolipin IgG | 27 | 22 | 2 | 3 | 0.37 |
| Anti-cardiolipin IgM | 24 | 20 | 3 | 1 | 0.79 |
| Anti-β2 glycoproteinI IgG | 16 | 10 | 6 | 0 | 0.006 |
| Anti-β2 glycoproteinI IgM | 4 | 3 | 1 | 0 | 0.34 |
| Anti-SSA Ab | 18 | 17 | 1 | 0 | 0.08 |
| Anti-SSB Ab | 11 | 9 | 2 | 0 | 0.39 |
| Low C3 | 12 | 8 | 1 | 3 | 0.04 |
| Low C4 | 16 | 11 | 2 | 3 | 0.14 |
| Anti-phospholipid syndrome | 14 | 11 | 2 | 1 | 0.98 |
| Medications, *n* (%) | | | | | |
| Prednisolone | 62 | 48 | 9 | 5 | 0.25 |
| Hydroxychloroquine | 15 | 10 | 3 | 2 | 0.19 |
| Azathioprine | 11 | 8 | 1 | 2 | 0.27 |
| Cyclosporin A | 3 | 0 | 2 | 1 | 0.001 |

SLE=Systemic lupus erythematosus, SLEDAI=Systemic lupus erythematosus disease activity index, SD=Standard deviation, ANA=Antinuclear antibody, Anti-ds DNA Ab=Anti-double stranded DNA antibody, IgG=Immunoglobulin G, IgM=Immunoglobulin M

They were classified into two groups of nephritis and non-nephritis according to the past history of LN. The former group was also categorized into clinical and biopsy proven nephritis subgroups. Clinical nephritis was approved in 14 patients and biopsy proven LN in 5 ones. No woman with biopsy-proven LN had class I pathology according to ISN/RPS. Class II, III, IV and VI were recorded in 1, 1, 2 and one patient (s), respectively. Their pregnancy terminated in preeclampsia, full term delivery with no complication, preeclampsia and abortion, respectively. They aged 26, 20, 24 and 24 and 33 years, respectively. The mean age of those with no LN was 28.7 years whereas the mean age of women with clinical nephritis was 26.1 years. The statistical difference was not significant. Table 2 shows that there was no significant difference in the mean age of SLE diagnosis in each pregnancy outcome among three groups; i.e., women with clinical nephritis, those with biopsy-proven LN and women with no LN. Similarly, there was no significant difference in the mean age of pregnancy in each pregnancy outcome, but preeclampsia, among the above-mentioned three groups.

### Adverse fetal and maternal outcomes

The findings of fetal and maternal outcomes are demonstrated in Table 3. No woman with LN experienced pre-term labor or stillbirth. 16 pregnancies either ended in abortion or experienced preeclampsia of which seven had LN. Eight cases experienced SLE flare and all had LN. Mean age (range) of SLE diagnosis in women with no complication, preeclampsia, abortion and pre-term labor was 22 (15-32), 20.5 (12-34), 23 (17-32) and 25.7 (21-30) years, respectively. Their statistical difference was not significant. The only patient with stillbirth had 20 year-old when diagnosed with SLE and 27 year-old at the time of stillbirth. Mean age (range) of women at the time of pregnancy in those with no complication, preeclampsia, abortion and pre-term labor was 27.8 (20-41), 28.7 (20-38), 28.3 (19-40), and 30.5 (27-35) years, respectively. Their statistical difference was no significant too. No ecclampsia, IUGR or neonatal death was recorded.

### Predictors of adverse fetal and maternal outcomes

Potential explanatory factors associated with adverse fetal and maternal outcomes revealed by univariate analyses are shown in Table 4. The presence of nephritis was associated with preeclampsia and combined pregnancy outcomes. SLEDAI scores before pregnancy and in the 3rd trimester were associated with preeclampsia. The area under curve (AUC) for SLEDAI during the 3rd trimester for preeclampsia was 0.8 (95% CI, 0.48-0.99). The optimal cut-off point according to the receiver operating characteristic (ROC) curve was 4.5, with the sensitivity of 75% and the specificity of 77%. Pre-term labors, which all

**Table 2:** Mean age of SLE diagnosis and pregnancy in various pregnancy outcomes occurred after SLE diagnosis compared among patients with clinical LN, biopsy-proven LN and without LN

| Mean age at the time SLE diagnosis (years) | Non-nephritis | Nephritis | | *P* value |
|---|---|---|---|---|
| | | Clinical | Biopsy proven | |
| No complication | 22 | 23.5 | 16 | 0.3 |
| Preterm labor | 25.7 | - | - | - |
| Preeclampsia | 27.5 | 16 | 17 | 0.09 |
| Abortion | 19 | 25 | 24 | 0.3 |
| Stillbirth | 20 | - | - | - |
| Unknown | 19 | 14 | - | - |
| Pregnancy (years) | | | | |
| No complication | 28 | 27 | 20 | 0.1 |
| Pre-term labor | 30.5 | - | - | - |
| Preeclampsia | 34 | 24.5 | 25 | 0.03 |
| Abortion | 24.5 | 27 | 33 | 0.3 |
| Stillbirth | 27 | - | - | - |
| Unknown | 28 | 26 | - | - |

SLE=Systemic lupus erythematosus, LN=Lupus nephritis

**Table 3:** Maternal and fetal outcomes in patients with and without lupus nephritis

| Characteristics | Total | Non-nephritis | Nephritis | | *P* value |
|---|---|---|---|---|---|
| | | | Clinical | Biopsy proven | |
| Pregnancy outcomes before SLE diagnosis, *n* (%) | | | | | |
| No pregnancy | 46 | 37 | 4 | 5 | 0.4 |
| No complication | 2 | 2 | 0 | 0 | |
| Abortion | 21 | 16 | 5 | 0 | |
| Stillbirth | 3 | 3 | 0 | 0 | |
| Pregnancy outcomes after SLE diagnosis, *n* (%) | | | | | |
| No complication | 44 | 38 | 5 | 1 | 0.09 |
| Pre-term labor | 7 | 7 | 0 | 0 | |
| Preeclampsia | 9 | 4 | 2 | 3 | |
| Abortion | 7 | 5 | 1 | 1 | |
| Stillbirth | 1 | 1 | 0 | 0 | |
| Unknown | 4 | 3 | 1 | 0 | |

SLE=Systemic lupus erythematosus

**Table 4:** Univariate analysis of the potential risk factors of adverse fetal and maternal outcomes

| | Pre-term labor | Abortion | SLE flare | Preeclampsia | Combined outcomes |
|---|---|---|---|---|---|
| Unadjusted odds ratio (95% CI) | | | | | |
| Age when diagnosed with SLE | 1.19 (1.001-1.4) | | 0.89 (0.8-0.99) | | |
| Number of pregnancies | | 2.34 (1.47-3.72) | | | 0.09 (0.016-0.49) |
| No past history of abortion | | 0.08 (0.026-0.24) | | | 0.056 (0.017-0.18) |
| SLEDAI before pregnancy | | | | 1.75 (1.03-2.98) | |
| SLEDAI, the 3rd trimester | | | | 1.78 (1.086-2.9) | |
| No nephritis | | | 0.05 (0.006-0.4) | 0.13 (0.03-0.59) | 0.145 (0.03-0.66) |
| ANA | | | | 7.6 (1.02-56.67) | |
| Normal C4 | | | | 0.19 (0.04-0.95) | |
| Anti-SSA Ab | | | 4.87 (1.28-18.57) | | |
| Cyclosporine administration | | | | 17.7 (1.42-221.1) | |

SLE=Systemic lupus erythematosus, 95% CI=95% confidence interval, SLEDAI=Systemic lupus erythematosus disease activity index, ANA=Antinuclear antibody

occurred in non-nephritis group, were associated with age of SLE diagnosis. The mean (range) age of this subgroup of patients was 25.7 (21-30) years. The AUC for age of SLE diagnosis of pre-term labor was 0.76 (95% CI, 0.63-0.89). The optimal cut-off point based on ROC curve was 24.5 years, with the sensitivity of 86% and the specificity of 71%. None of the administered medications including hydroxychloroquine had a significant association with any adverse outcome. The only exception was cyclosporine [Table 4].

Multivariate logistic regression analyses demonstrated independent explanatory factors linked to combined maternal and fetal outcomes [Table 5]; i.e., past history of abortion and nephritis. Further analyses revealed nephritis and positive ANA were associated with preeclampsia, older age of SLE development was related to pre-term labor and finally, past history of abortion was associated with abortion.

## DISCUSSION

14 patients with SLE had renal involvement during pregnancy in our study. This was less than that reported in studies conducted in Hong Kong[22] (30 out of 55 pregnancies) or Saudi Arabia[23] (73 out of 176 pregnancies). Similarly, the mean age of our patients at the time of pregnancy was lower than those in the above-mentioned studies (30.2 and 36.4 years, respectively).[22,23] The current study demonstrated that the lack of LN had

**Table 5:** Independent explanatory variables associated with adverse fetal and maternal outcomes

| Fetal and maternal outcomes | *P* value | Odds ratio | 95% CI |
|---|---|---|---|
| SLE flare | | | |
| No nephritis | 0.01 | 0.06 | 0.007-0.56 |
| Preeclampsia | | | |
| No nephritis | 0.03 | 0.04 | 0.002-0.69 |
| ANA | 0.03 | 30.15 | 1.4-645 |
| Abortion | | | |
| No past history of abortion | 0.0001 | 0.08 | 0.026-0.24 |
| Pre-term labor | | | |
| Age when diagnosed with SLE | 0.049 | 1.2 | 1.001-1.4 |
| Combined outcomes | | | |
| No past history of abortion | 0.0001 | 0.06 | 0.017-0.18 |
| No nephritis | 0.02 | 0.17 | 0.036-0.78 |

95% CI=95% Confidence interval, SLE=Systemic lupus erythematosus, ANA=Antinuclear antibody

protective role against SLE flare, preeclampsia and combined adverse maternal and fetal outcomes. LN has been shown to be associated with adverse maternal outcomes in many investigations.[9,22-25] Although in Al Arfaj *et al.* study,[23] there was a significant association between LN and pre-term labor, all seven pre-term labors in the current study occurred in SLE patients with no LN. In other words, we found no relationship between LN and pre-term labor. The only variable found significantly associated with pre-term labor was the age of mother at the time of SLE diagnosis. Higher the age of SLE diagnosis higher is the possibility of pre-term labor. Abortion rate in our study was 10%, which was in the range of 8-24% reported by other studies.[26-29] Lack of past history of abortion had protective role against abortions in the current pregnancies, but the anti-phospholipid syndrome revealed no relationship with fetal loss. The rate of positive anti-SSA Ab in the study conducted in Saudi Arabia[23] was 44%, whereas in the current study, it was 25%. This might explain why Al Arfaj *et al*.[23] found a significant association between pre-term labor and anti-SSA Ab, whereas we found no association. Low C3/C4 had no association with pre-term labor in the current research and Al Arfaj *et al.* study.[23] Hydroxychloroquine administration had no protective effect on adverse fetal/maternal outcomes. The same was revealed in the study conducted in Saudi Arabia,[23] whereas the reverse was shown in Hong Kong study.[22] The only medication, which demonstrated significant relationship with preeclampsia was cyclosporine. This might be due to cyclosporine induced hypertension.

There were some limits in the current study. Presence or absence of hypertension was not recorded. Hypertension is one of the risk factors for adverse fetal and maternal outcomes. The retrospective nature of the current cohort study didn't let us follow the babies for other complications such as prematurity and small for gestational age. Only 19.5% of pregnancies experienced LN. Then, complete and in depth evaluation of the relationships of LN and different outcomes were not possible. Execution of this study in multi-centers when the above-mentioned limits are removed may improve our understandings about the preventive measures on the impacts of LN on mothers and babies during pregnancy period and afterward.

## CONCLUSIONS

The current study revealed that when LN is not present in pregnant patients with SLE, preeclampsia and SLE flare will be less likely to occur.

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