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# Outcomes of planned pregnancy in patients with systemic lupus erythematosus and their neonates

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ABSTRACT

*Aim of the work:* To assess the outcome of planned pregnancies in patients with systemic lupus erythematosus (SLE). Patients and methods: The study was conducted on 32 patients. The medical management included pre-pregnancy planning at the quiescent phase of the disease and after at least six months of clinical remission. The patients had a monthly visit during pregnancy and three months post-delivery. Disease flare was characterized by the recurrence of symptoms and signs in different organs, as well as the need for an increase in medication dose. Results: There were 36 planned pregnancies in 32 patients, of which 15 and 17 cases were primiparous and multiparous, respectively. The SLE flares were observed in 36.1% of the cases, 8.3% of which developed postpartum; moreover, they were moderate in severity and mostly involved the kidneys and joints. Pregnancy outcomes included18 (50%) cases ended in term labor; 13 (36.1%) pregnancies had preterm labor, and 5 (13.8%) pregnancies terminated with abortions. Furthermore, obstetric complications included 2(6.5%) patients with premature rupture of membranes, 5(15.6%) fetuses with intrauterine growth retardation, and 2(6.4%) mothers with preeclampsia. 10(27.7%) pregnancies occurred in patients with lupus nephritis. Cesarean section was performed on 24(77.4%) patients, and low birth weight was observed in 7(21.8%) infants. None of the infants had neonatal lupus, congenital deformities or infection. Conclusion: Pre-pregnancy planning in patients with SLE can considerably improve pregnancy outcomes. Neonatal lupus, congenital anomalies or infection were not present. SLE patients intending to become pregnant should be provided with close medical supervision for a safe maternal and fetal outcome.


## 1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting females of reproductive age [1–3] and these patients are at high risk for adverse pregnancy outcomes (APOs) compared to the healthy population. However, controversial outcomes are reported by multiple studies that have been performed to determine the impact of SLE on pregnancy [2,4–10]. The association between SLE and poor pregnancy prognosis has been reported while improved outcomes have also been shown with a live birth rate in at least 85% of the pregnancies [11]. In this regard, most research conducted on the association between pregnancy and SLE has confirmed an increased risk for both mother and fetus, particularly when the disease is active. Pregnancy in patients with SLE is associated with a higher risk of abortion, fetal death, premature birth, hypertension, venous thromboembolism, preeclampsia, eclampsia, intrauterine growth retardation, and neonatal lupus syndrome [5,12]. On the other hand, fetal outcomes are relatively favorable in patients with stable or mild activity [2,13].

In order to prevent such potential risks, the pregnant patient should be under the supervision of a medical team consisting of a rheumatologist, an obstetrician, and a sonographer [14]. It is recommended that patients with SLE be pregnant during the inactive or stable phase of the disease, which is called "planned pregnancy"

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[12,15]. Moreover, females with SLE should only be allowed to conceive when their disease is in the clinically quiescent phase [11].

The effect of SLE on fetal and maternal prognoses is not completely understood; moreover, it is of critical importance to evaluate the patients to predict the possible risks. Therefore, the present study aimed to assess the outcomes of planned pregnancies in patients with SLE.

## 2. Patients and methods

This retrospective study was conducted on a cohort of SLE patients fulfilling the 1997 American College of Rheumatology updated revised classification criteria [16] presenting to the Rheumatology Clinic of Ghaem Hospital, Mashhad, Iran, between 1999 and 2012. The study protocol was approved by the Research Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. All patients were informed about the research objectives and procedure and an informed consent was obtained.

The medical management included pre-pregnancy planning at the quiescent phase of the disease and after at least six months of clinical remission. The patients had a monthly visit during pregnancy and three months post-delivery. Immune profile tests included antiphospholipid antibodies, lupus anticoagulant, antinuclear antibodies (ANA), anti-double strand deoxyribonucleic acid (anti-ds DNA), complement (C3 and C4), anti-SSA (Ro), and SSB (La).

Disease flare was characterized by the recurrence of symptoms and signs in different organs, as well as the need for an increase in medication dose. Maintenance doses of the medications received by the patients at the initiation of their pregnancy were continued by the majority throughout the study. Doses of prednisolone, hydroxychloroquine, and/or azathioprine were adjusted according to flares severity with consequent decrease when controlled. Daily aspirin (100 mg/day) was administered to patients positive for anti-cardiolipin and/or lupus anticoagulant. Heparin was used for those with a prior history of a thromboembolic event. Patients with lupus nephritis (LN) received monthly cyclophosphamide injections for 3–6 months followed by monthly Gonadotropin-releasing hormone (GnRH) therapy and were maintained on mycophenolate mofetil (upto 2 g/day) and prednisolone with at least 6 months of disease quiescence before conception.

An echocardiogram of the fetal heart was performed on the 18th and 30th weeks in those with positive anti-SSA and SSB antibodies to identify any existing heart block.

*Statistical analysis:* Statistical Package for the Social Sciences (SPSS) version 22 was used. Data was presented as mean ± SD or frequency and percentage. Student's *t*-test and Chi-square test were considered for comparison. A p-value < 0.05 was considered significant.

## 3. Results

There were 36 planned pregnancies in 32 patients of which 15 and 17 cases were primiparous and multiparous, respectively (4 cases had two pregnancies each). Table 1 presents the demographic and clinical characteristics of the patients in the present study. The SLE flares were observed in 13 (36.1%) cases; during pregnancy in 10 (27.8%) and postpartum in 3 (8.3%). Table 2 presents the manifestations of the disease flares. No abortion was reported in cases with flares. In all cases, flares were of moderate severity except 1 case with late thrombocytopenia (platelets: 37,000/mm$^3$) reported in the second trimester, and the pregnancy was terminated with severe preeclampsia in the 30th week. The newborn weighed 0.7 kg and died after three months in the Intensive Care Unit (ICU) sustaining massive pleural effusion.

Of the 36 planned pregnancies, 18 (50%) cases ended in term labor with a mean gestational age of 38 ± 0.7 weeks; moreover, 13 (36.1%) pregnancies, including a twin pregnancy, had preterm labor with a mean gestational age of 34.9 ± 1.6 weeks, and 5 (13.8%) pregnancies terminated with abortions. 5 abortion occurred in 4 patients during the quiescent phase of the disease while the patients were on medications. Furthermore, there were two early spontaneous abortions in weeks 7 and 9 in one patient. In both cases, the fetus did not yet have a heart. Another abortion occurred in a patient with antiphospholipid syndrome (APS) and prior history of four spontaneous abortions before the 7th gestational week and a still death occurring in the 30th week. In the remaining two abortions, it was not possible to identify any causes. 7th

In the present study, successful pregnancies were observed in 31 cases. Cesarean section (CS) was performed on 24 (77.4%) which was elective or due to preeclampsia, premature rupture of membranes, cephalopelvic disproportion, and previous CS, while only 7 (22.6%) had normal vaginal deliveries. 10 (27.8%) cases had history of LN previously managed; 7 (70%) of them had medically-controlled hypertension, while only 3 (14.3%) of those without LN had medically-controlled hypertension. Disease flare occurred in 5 (50%) LN patients during pregnancy (n = 4) and after delivery

**Table 1**
Demographic and clinical characteristics of systemic lupus erythematosus patients with planned pregnancies.

| Variables mean ± SD or n(%) | | Pregnancies in SLE (n = 36) | |
|---|---|---|---|
| Age (years) | | 31 | ±7 |
| Disease duration (years) | | 7.9 | ±3.9 |
| Age at onset (years) | | 23.1 | ±5.3 |
| Disease onset till pregnancy (years) | | 4.5 | ±3.03 |
| Type of pregnancy | Single pregnancy | 35 | (97) |
| | Twin pregnancy | 1 | (3) |
| Coexisting disease | Antiphospholipid syndrome | 2 | (6.2) |
| | Lupus cerebritis | 2 | (6.2) |
| | Idiopathic thrombocytopenic purpura | 2 | (6.2) |
| | Lupus nephritis | 10 | (31.2) |
| | Prior thrombophlebitis | 2 | (6.2) |
| Medications used | Prednisolone | 29 | (80.5) |
| | Hydroxychloroquine | 28 | (77.7) |
| | Azathioprine | 5 | (13.8) |
| Antibodies | Anticardiolipin | 2 | (6.2) |
| | Anti-smooth muscle | 13 | (40) |
| | Anti-SSA | 7 | (21.6) |
| | Anti-SSB | 1 | (3.6) |

**Table 2**
Manifestations of disease flares in pregnant systemic lupus erythematosus patients.

| Flare in pregnant SLE patients (n = 13) | | | | |
|---|---|---|---|---|
| Period | n (%) | Manifestations | n (%) | |
| First trimester | 2 (15.3) | Joint | 2 | (13.3) |
| | | Mucocutaneous | 1 | (6.6) |
| Second trimester | 2 (15.3) | Renal | 1 | (6.6) |
| | | Thrombocytopenia | 1 | (6.6) |
| Third trimester | 6 (46.1) | Renal | 4 | (26.6) |
| | | Joint | 2 | (13.3) |
| | | Mucocutaneous | 1 | (6.6) |
| Postpartum | 3 (23.1) | Joint | 1 | (6.6) |
| | | Mucocutaneous | 1 | (6.6) |
| | | Thrombocytopenia | 1 | (6.6) |

**Table 3**
Gestational age and weight of newborns with and without flare and lupus nephritis.

| Variables mean ± SD | All neonates(n = 31) | Flare (n = 13) | no flare (n = 18) | p | LN (n = 5) | No LN (n = 8) | p |
|---|---|---|---|---|---|---|---|
| Gestational age (wks) | 36.7 ± 1.9 | 35.2 ± 2.1 | 37.4 ± 1.5 | **0.002** | 36.6 ± 1.4 | 36.7 ± 2.2 | 0.88 |
| Birth weight (kg) | 2.7 ± 0.67 | 2.42 ± 0.78 | 2.83 ± 0.61 | 0.12 | 2.63 ± 0.65 | 2.73 ± 0.71 | 0.72 |

LN: lupus nephritis. Bold values are significant at $p < 0.05$

**Table 4**
Complications in systemic lupus erythematosus patients with successful delivery.

| Complication n (%) | Successful delivery in SLE (n = 31) | |
|---|---|---|
| Preeclampsia | 2 | (6.5) |
| Intrauterine growth retardation (IUGR) | 5 | (15.6) |
| Premature rupture of membranes (PROM) | 2 | (6.5) |
| Pregnancy-induced hypertension (PIH) | 2 | (6.5) |
| Gestational diabetes | 2 | (6.5) |
| Antiphospholipid syndrome | 2 | (6.5) |

(n = 1). Preterm labor developed in 4 (40%) LN patients with a mean gestational age of 35.3 ± 0.95 weeks and a mean newborn weight of 2.2 ± 0.69 kg (1.1 2.8 kg). Table 3 presents gestational age and weight of neonates in SLE with and without flare and LN.

Table 4 summarizes the pregnancy complications in patients with successful pregnancies. None of the successful pregnancies were complication-free, and no HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome was observed. One of the cases with APS had a history of deep venous thrombosis (DVT), six early spontaneous abortions before 7th gestational week, and one stillbirth in the 30th gestational week. 4 or 6. Despite prophylaxis with aspirin 100 mg/day and heparin 5000 IU twice daily, she had an abortion in the 6th week of pregnancy. Another patient presented with history of late spontaneous abortion (19th gestational week) and tested positive for antiphospholipid autoantibodies and was treated with aspirin 100 mg/day and heparin 1000 IU/day or enoxaparin 40 mg/day. Fortunately, her pregnancy ended with the term labor of a newborn weighing 3.15 kg. Of the total 36 pregnancies, one patient developed LN in the third trimester and another immediately after delivery (proteinuria > 0.5 g/day).

There were 7 (21.9%) newborns with low birth weight (LBW) (<2.5 kg) and a mean weight of 1.71 ± 0.65 kg (0.7–2.4 kg). 6 (18.8%) of the newborns were in the ICU; 3 of whom had LBW. Other causes of LBW included hypoglycemia (n = 1), disorder of Rhesus (n = 1), and jaundice (n = 2). There were no cases of neonatal lupus among our patients. It is worth mentioning that there were also no reports on congenital abnormalities, infection, or neonatal deaths.

## 4. Discussion

Pregnancy in patients with SLE along with the effect of pre-pregnancy planning on disease activity, as well as maternal and fetal outcomes has always been a popular area of research, especially in the field of rheumatology. During pregnancy, the clinical condition of such patients may deteriorate [17–19]. An increase in the SLE activity during pregnancy, as well as maternal and fetal complications, are two major concerns among pregnant women with SLE [20–22].

Out of 36 planned pregnancies in 32 patients in the present study, disease flare occurred in 36.1% of the cases; during pregnancy in 27.8% and after delivery in 8.3%. Disease flare may occur at any time during pregnancy and the postpartum period [9,22–24]. In the present study, 46.2% of the disease flares occurred in the third trimester. The most common manifestations of the disease flares were renal and joint involvement in 38.5% of patients. The risk of developing a flare seems to be associated with disease activity 6–12 months before conception. As expected, an active disease state during this period increases the patient's chances of developing a disease flare, while those with their disease in remission have lower chances [9,25,26].

In this study, flares were moderate in severity and were controlled by adjusting the medications dose without the need for hospital admission. Similar results were obtained in previously studies [6,9,14,27]. A good prognosis is expected in mild forms with good control over disease activity.

No relation was found between the SLE flare and abortion in this study as every case of abortion was clinically inactive. Similar findings were reported in a study conducted by *Carmano et al.* They indicated that 5/13 cases with flares occurred in patients with controlled LN, and the other eight cases developed in patients without LN. In the aforementioned study, half of the patients with LN suffered from flares during pregnancy, whereas only 24% of the patients without renal were active [28]. Similarly, in pregnant SLE patients with LN, a poor outcome was reported in 62.5% compared to a normal outcome in 35.7% [29]. On the other hand, some studies showed a higher risk of abortion in females with an SLE experience [5,30]. Patients with LN have a higher tendency towards developing flares [31,32] while *Ideguchi et al.* [9] found no difference.

Preterm labor developed in 40% of patients with LN and may suggest an association with and this was in agreement to another study [33]. However, *Carmona et al.* and *Huong et al.*, observed no association between SLE and preterm labor [28,34]. It is worth noting that the majority of patients in this work were on prednisolone therapy throughout their pregnancy.

Based on the results, gestational age at birth was significantly lower in mothers with disease flares during pregnancy, compared to those without. In accordance, *Skorpen et al.,* reported an increased LBW and preterm birth in SLE patients and was amplified by an active disease [35].

Another important question was the association between APS and fetal death. APS has been considered a strong risk factor for fetal mortality [28,36–39]. The two patients with APS in this work had significant history of fetal death with seven abortions and one stillbirth. However, only one of the planned pregnancies with APS ended with abortion. REVISE 4,7,8 in APS

Regarding the gestational age at birth, no significant difference was observed between infants of mothers suffering from LN and those without which is in line with the study conducted by *Ideguchi et al.* [9]. In another study [28], the gestational age at birth was significantly lower in mothers with LN compared to those without. An increase in live births and a decrease in abortion rates among patients with planned pregnancies have been reported in pervios studies [11,19,40]. Additionally, 7/10 pregnant patients with LN had hypertension, while only 3/21 without renal disease were hypertensive. The major risk factors for fetal death (i.e. abortion and stillbirth) in pregnant SLE patients include APS, hypertension in mothers, proteinuria, and thrombocytopenia.

Regarding the study limitations are the lack of a disease activity score and the small size.

In conclusion, pre-pregnancy planning in patients with SLE can considerably improve pregnancy outcomes and result in similar live-birth rates to those of the normal population; however, the incidence of preterm labor remains high especially in those with disease flares. Close monitoring of patients with SLE before conception and monthly during pregnancy may lead to better outcomes for both mother and infant.

## 5. Ethical considerations

The study protocol was approved by the Research Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran. Before the study, the research objectives and procedures were explained to all patients, and informed consent was obtained from them. Moreover, they were assured that their information would remain confidential and they could withdraw from the study at any time.

## 6. Consent for publication

Not applicable.

## 7. Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Author contributions

This work was carried out in collaboration among all authors. ZRY designed the study, performed the statistical analysis, MKH wrote the protocol, and wrote the first draft of the manuscript. HJ and MM managed the analyses of the study. ZY managed the literature searches. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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