Outcomes of Pregnancies Complicated by Systemic Lupus Erythematosus (SLE)

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Objective: *To assess the outcomes of pregnancies complicated by systemic lupus erythematosus (SLE) and evaluate the clinical course of the disease during pregnancy.*
Material and Method: *The database of high-risk pregnancies between 1995 and 2006 was prospectively collected and searched for pregnancies with SLE. The medical records were reviewed.*
Results: *Sixty-eight pregnant women were identified during the period of the present study. Of 61 (89.7%) live births, 27 (39.7%) had preterm delivery and 20 (29.4%) had fetal growth restriction. Mean gestational age was 35.6 $\pm$ 4.2 weeks. Mean neonatal birth weight was 2322 $\pm$ 781 grams. There were seven (10.3%) perinatal deaths. Maternal SLE flares occurred in 20 (29.4%), seven in the first trimester, eight in the second trimester, five in the third trimester, and none in the post partum period. Preeclampsia is the most common maternal complication (20.6%). There was a higher rate of flares if the pregnancy occurred while the disease was active. The predictor of poor pregnancies outcomes included flare-up of the disease, renal involvement, hypertension, and conception while the disease is active.*
Conclusion: *Active SLE prior to pregnancy is associated with a less favorable maternal and fetal outcome. Hypertension increased the risk of fetal loss and adverse outcome.*

Keywords: *Systemic lupus erythematosus, Pregnancy, Outcome*

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Systemic lupus erythematosus (SLE) is a multisystem auto-immune disease that predominantly affects women in their childbearing years. Therefore, pregnancies and its outcomes are of particular importance in this condition. Many studies have shown that there is an increased risk of flare of disease during pregnancy. Rate of pregnancy flare of SLE is in the range of 13.5% to 65%[1-10]. Fetal outcome may also be jeopardized in lupus pregnancy, with higher than normal rates of spontaneous abortion, stillbirth, preterm delivery, fetal growth restriction (FGR), and fetal loss rates[1,3,4,6,9,11-16]. There is also an increased risk of pre-eclampsia and gestational hypertension[17,18].

Data on pregnancy outcome from Asian people is very scanty. Hence, the authors analyzed the outcomes of pregnancy in the presented Thai patients with SLE.

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Material and Method

Data regarding the pregnancies were collected retrospectively from January 1999 to December 2006 at Maharaj Nakorn Chiang Mai Hospital, a tertiary care center. All patients were diagnosed and taken care of by their rheumatologist and attended the antenatal care clinic regularly during their pregnancies. The collecting data were disease-related manifestations, comorbidities, obstetrics complications, and laboratory investigation. All patients satisfied the revised 1982 American College of Rheumatology (ACR) classification criteria for SLE[19]. A flare was defined as if they 1) had increasing symptoms or signs in the organs involved, 2) required more dosage of corticosteroids, and 3) were being considered by the rheumatologist team. At each assessment, symptoms and physical findings, particularly in those organs involved with SLE were recorded. Laboratory investigation at the diagnosis of pregnancy included complete blood counts, serum VDRL, blood group, Rh typing, anti- HIV test, thalassemia screening, and urinary analysis were carried out. Additional

laboratory tests, e.g. serum complement levels, biochemical profiles and a 24-hr urine protein determination were done if clinically indicated. Anticardiolipin (aCL), antibodies to Ro (SSA) and anti-La (SSB) were not available at Chiang Mai Hospital.

Definitions of pregnancy outcomes were as follows: spontaneous abortion - spontaneous loss of a fetus before 20 weeks of gestation; stillbirth - death of a fetus *in utero* after 20 weeks of gestation; premature birth (preterm) - live birth before 37 weeks of gestation; and fetal growth restriction (FGR) - birth weight below the 10th percentile of the normal growth curve; preeclampsia - evidence of proteinuria ($\geq$ 300 mg/24 hours) or > 1+ by dipstick and hypertension, with or without edema, in patients with normal blood pressure and no evidence of proteinuria prior to 20 weeks of gestation, or a significant increase in blood pressure and proteinuria or new abnormalities in platelet count or liver enzyme levels in the presence of preexisting hypertension and proteinuria; gestational hypertension - systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg without evidence of proteinuria.

Statistical analysis

The data were analyzed using the statistical package for the social sciences (SPSS). Descriptive statistics mean $\pm$ standard deviation, range and number (%), the X^2 test, Fisher's exact test and Student's *t* test were used as appropriate Relative Risk (RR) and 95% confidence interval (95%CI) were used to predict the maternal and fetal adverse outcome. Statistical significance was set at $p < 0.05$.

Results

During the study period, 68 pregnant women were diagnosed for SLE. Thirty had one pregnancy, 22 had two, and 16 had three or more. None was multifetal pregnancy. The mean ($\pm$ SD) age at conception was 28.1 $\pm$ 5.7 years, ranged 19-41 years. Mean disease duration prior to the current pregnancy was 4.3 $\pm$ 3.1 years. Of all, seven (10.3%) were first time diagnosed for SLE during pregnancy, whereas 61 (89.7%) had known diagnosis prior to the current pregnancy. Of the known cases before pregnancy, 11 (16.2%) women had an uncontrolled disease at conception, while the remaining 50 (73.5%) became pregnant during a remission period of the disease. Among 20 patients with flare-up disease during pregnancy, eight had renal disease, seven had hemolytic anemia, and five had mild and involved skin or joints or serositis.

Maternal outcomes

The frequency of SLE flare-up during pregnancy was observed in 20 pregnancies (29.4%). Seven occurred in the first trimester, 8 in the second trimester and 5 in the third trimester. No flare occurred during the post partum period. The most common organ disorders that were associated with flare-ups were renal involvement and hematological abnormalities (Table 1). Maternal obstetric complications were the preeclampsia (20.6%), hypertension (13.2%), and infection (Table 2). There was no case of maternal death in the present series.

Fetal outcomes

Of the 68 pregnancies, 4 (5.9%) were terminated because of severe active disease. Three (4.4%) died *in utero* due to active maternal lupus, hypertension with placental abruption and severe preeclampsia, respectively. Total live birth 61 (89.7%) pregnancies, 27 (39.7%) were preterm delivery and 34 (50%) were term delivery. Mean gestational age was 35.6 $\pm$ 4.2 weeks. Mean neonatal birth weight was 2322 $\pm$ 781 grams. Of live births, 20 (29.4%) had intrauterine growth restriction. There were seven (10.3%) perinatal deaths. There was no case of neonatal lupus or congenital complete atrioventricular block.

Discussion

SLE during pregnancy has a high rate of adverse outcomes, including preterm delivery, pregnancy-induced hypertension, fetal growth restriction, and perinatal death. Interestingly, active disease during

Table 1. Organ flares in 68 pregnancies

Involved organ	No. (%)
Renal	8 (11.8)
Hematologic	7 (10.3)
Arthritis / arthralgia	2 (2.9)
Serositis	2 (2.9)
Mucocutaneous	1 (1.5)

Table 2. Maternal obstetric complications in 68 pregnancies

Complication	No (%)
Hypertension	9 (13.2)
Preeclampsia	14 (20.6)
Infection	11 (16.2)

pregnancy is associated with a higher rate of adverse outcomes than that in inactive cases.

Like several previous reports[10,16,20], activity of the disease at conception was associated with a higher rate of flare-up, as well as pregnancy outcomes. The authors found that conception while the disease was active had a tendency to have a worse outcome than that occurring during the remission of the disease, though the difference was not statistically significant which might be due to too small a sample size (Table 3).

The rate of FGR among the live-birth pregnancies in the present cohort was rather high (29.4%) compared to the incidence in general obstetric population. However, it is comparable with that reported in other series of pregnancy with SLE which ranged between 13-40%[3,21,22] Surprisingly, although the FGR rate has a tendency of an increase in the women with active disease or renal involvement, compared to that in the group without active disease or renal involvement, it is not significantly different. This suggests that pregnancy with SLE had an increase in risk of FGR, regardless of activity or renal involvement.

Based on the findings in the present study, SLE during pregnancy is associated with higher rates of maternal complications, especially preelcampsia and flare-up of the disease and adverse fetal outcomes including preterm delivery, fetal growth restriction, and stillbirth. Pregnancy occurring during the remission of the disease had less chance of flare-up during pregnancy (Table 3). Moreover, women with active disease during pregnancy have a higher rate of adverse outcomes than those with inactive disease (Table 4). The authors support that all pregnant patients with SLE must be carefully monitored throughout pregnancy by expert rheumatologists and obstetricians, especially the cases with active disease at the beginning of pregnancy and exacerbation of disease must be immediately detected and controlled.

Table 3. Complications and remission and non-remission disease at conception

Complications	Non-remission (11)	Remission (50)	p-value
Flare	6	14	0.001
Preeclampsia	6	16	0.159
Preterm delivery	5	18	0.558
Fetal growth restriction	2	15	0.857
Perinatal mortality	3	4	0.069
Infection	1	10	0.394

Table 4. Complications in patients with active and inactive disease during pregnancy

Complications	Active (27)	Inactive (41)	p-value
Preeclampsia	13	10	0.020*
Preterm delivery	17	10	0.001*
Fetal growth restriction	9	11	0.565
Stillbirths	6	0	0.001*
Infection	3	8	0.357

* Pearson Chi-square

Unfortunately, in the early part of the present study, some laboratory work-ups were not available in Chiang Mai Hospital, including anticardiolipin antibody, SS-A, and SS-B, which are commonly present in SLE. In a prospective study[23], SS-A and SS-B antibody was associated with neonatal lupus or congenital heart block, but had no effect on other pregnancy outcomes. Although, the authors did not test for SS-A or SS-B in all cases, none of the live-birth infants in this series had either neonatal lupus or congenital complete atrioventricular block.

Table 5. Predictors of maternal and fetal adverse outcome in 68 pregnancies

Predictor	Present	Absent	RR (95% CI)	p-value
Renal disease (19/68)				
Maternal complication	12/19	12/49	5.30 (1.7;16.5)	0.003
Fetal adverse effects	4/19	19/49	2.37 (0.68;8.4)	0.166
Hypertension (9/68)				
Perinatal death	5/9	2/59	2.50 (1.2;6.4)	<0.001
Active disease (27/68)				
Maternal complication	14/27	10/41	3.30 (1.2;9.4)	0.020
Fetal adverse effects	12/27	11/41	1.65 (0.9;2.76)	0.133

Surprisingly, postpartum flare-ups of SLE have been noted in several studies, the present study does not show an increase in such a problem. This should be further elucidated with further study with a larger sample size in the presented population.

Studies from developed countries have shown that the outcome of pregnancy has improved significantly in recent years. Fetal loss in prospective studies is 11-28%[3,18]. The fetal loss in SLE mothers is still higher when compared with matched healthy women due to higher incidences of spontaneous abortions, stillbirth, and prematurity[12,18,24]. Based on the present study, though the fetal loss is still rather higher, the live birth of 89.7% seems to be similar to that reported from the Western world and this is a higher rate than that recently reported from India (58.7%)[16].

The occurrence of live births in the subset of patients with inactive disease is comparable with published rates from Western countries. The only variable that was significantly associated with an adverse maternal and fetal outcome was active disease at conception or during pregnancy. Active disease at conception is a known predictor of poor outcome[3,17,18].

As in the study reported by Huong, et al[17], SLE nephritis or the disease with renal involvement is strongly related to pregnancy-induced hypertension and has a tendency to increase poor fetal outcomes, though it is not significantly increased. This might be due to small sample size showing such a low fetal death rate.

On the other hand, the live birth rate in the presented patients with inactive disease had very good outcomes. This reflects that these patients had planned pregnancies, which have previously been shown to have a better outcome[25].

In conclusion, the present study suggests pregnancy is safe in most lupus patients who conceive while the disease is inactive. Active SLE prior to pregnancy is associated with a less favorable maternal and fetal outcome. Hypertension may increase the risk of fetal loss and adverse outcome.

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ผลการตั้งครรภ์ของสตรีตั้งครรภ์ที่เป็นโรคเอสแอลอีที่โรงพยาบาลมหาราชนครเชียงใหม่

พจนีย์ ผดุงเกียรติวัฒนา, พรรณี ศิริวรรธนาภา, ธีระ ทองสง

วัตถุประสงค์*: เพื่อศึกษาผลลัพธ์ของการตั้งครรภ์ และประเมินการดำเนินโรคเอสแอลอี ในขณะตั้งครรภ์ ของสตรีตั้งครรภ์ที่เป็นโรคเอสแอลอี*

วัสดุและวิธีการ*: ทำการศึกษาแฟ้มประวัติสตรีตั้งครรภ์ที่เป็นโรคเอสแอลอี ที่มารับการรักษาแบบครรภ์เสี่ยงสูง ระหว่างเดือนมกราคม พ.ศ. 2538 ถึงเดือนธันวาคม พ.ศ. 2549*

ผลการศึกษา*: จากสตรีตั้งครรภ์ที่เป็นโรคเอสแอลอีที่มาคลอดบุตรที่โรงพยาบาลมหาราชนครเชียงใหม่ทั้งสิ้น 68 ราย คลอดทารกมีชีพ 61 ราย (ร้อยละ 89.7) คิดเป็นทารกที่คลอดก่อนกำหนด 27 ราย (ร้อยละ 39.7) ทารกโตช้าในครรภ์ 15 ราย (ร้อยละ 22.1) ตายปริกำเนิด 7 ราย (ร้อยละ 10.3) อายุครรภ์เฉลี่ย 35.6 $\pm$ 4.2 สัปดาห์ น้ำหนักทารกแรกคลอดเฉลี่ย 2,322 $\pm$ 781 กรัม ขณะตั้งครรภ์มีการกำเริบของโรคเอสแอลอี 20 ราย (ร้อยละ 29.4) พบการกำเริบในไตรมาสแรก 7 ราย ไตรมาสที่สอง 8 ราย และไตรมาสที่สาม 5 ราย ไม่พบการกำเริบในช่วงหลังคลอด ภาวะแทรกซ้อนจากครรภ์เป็นพิษ เป็นภาวะแทรกซ้อนที่พบได้บ่อยที่สุด ร้อยละ 20.6*

สรุป*: การตั้งครรภ์ในขณะที่โรคเอสแอลอียังควบคุมไม่ได้ การที่มีภาวะแทรกซ้อนทางไตจากโรคเอสแอลอี ภาวะความดันโลหิตสูง และการกำเริบของโรคเอสแอลอีในขณะตั้งครรภ์ เป็นปัจจัยสำคัญที่จะทำนายถึงผลลัพธ์การตั้งครรภ์ที่ไม่ดี ส่งผลเสียต่อการตั้งครรภ์ ทั้งสตรีตั้งครรภ์และทารกในครรภ์*