

Risk Factors for Poor Pregnancy Outcome in Systemic Lupus Erythematosus Patients

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ABSTRAK

Latar belakang: lupus eritematosus sistemik (LES) merupakan penyakit autoimun kompleks yang membutuhkan penanganan khusus, terutama saat kehamilan. Kesadaran akan faktor-faktor yang menyebabkan luaran kehamilan yang buruk penting untuk optimalisasi luaran kehamilan pada pasien LES. Penelitian ini bertujuan memberikan gambaran mengenai luaran kehamilan dan faktor risiko yang berhubungan dengan buruknya luaran kehamilan pada pasien LES. **Metode:** penelitian kasus-kontrol retrospektif dilakukan pada pasien LES dengan berbagai luaran kehamilan. Riwayat dan komplikasi kehamilan diketahui dari data registri lupus di Rumah Sakit Umum Pusat Dr. Hasan Sadikin Bandung. Kelompok kasus berupa kehamilan dengan luaran yang buruk; yaitu aborsi, kelahiran prematur, lahir mati, pertumbuhan janin terhambat (PJT), dan kematian neonatal. Kelompok kontrol berupa kehamilan dengan luaran yang baik yakni lahir hidup dan cukup bulan. **Hasil:** Total 84 pasien LES terlibat di dalam penelitian ini dengan 109 data kehamilan setelah diagnosis LES. Median usia subjek pada saat kehamilan adalah 28 (25-32) tahun. Luarannya kehamilan yang buruk terdiri dari 22,9% abortus, 14,7% kelahiran prematur, 5,5% lahir mati, 1,8% PJT, dan 4,6% kematian neonatal. Kelompok kasus dan kontrol memiliki perbedaan yang bermakna dalam hal jumlah kehamilan terencana ($P=0,011$). Luarannya kehamilan yang buruk dalam penelitian ini berhubungan dengan lupus nefritis ($OR = 4,813, 95\% CI 1,709 - 13,557, P = 0,003$) dan SLE neuropsikiatri ($OR = 5,045, 95\% CI 1,278 - 19,920, P = 0,021$). **Kesimpulan:** perencanaan kehamilan diperlukan untuk mendapatkan luaran kehamilan yang lebih baik. Nefritis dan neuropsikiatri lupus merupakan faktor risiko bagi terjadinya luaran kehamilan yang buruk.

Kata kunci: lupus eritematosus sistemik, kehamilan, luaran buruk.

ABSTRACT

Background: systemic lupus erythematosus (SLE) is still a challenging autoimmune disease, especially in pregnancy setting. An early risk factors awareness of poor pregnancy outcome is important to optimize the outcome of pregnancy in SLE patients. This study was conducted to describe pregnancy outcome and determine the risk

factors associated with poor pregnancy outcome in SLE patients. **Methods:** a retrospective case-control study of SLE patients with poor and normal pregnancy outcome was performed. Pregnancy histories were reviewed from Dr. Hasan Sadikin General Hospital lupus registry study. The case group was pregnancy with poor outcome, defined as abortion, premature birth, stillbirth, intrauterine growth restriction (IUGR) and neonatal death. The control group was pregnancy with good outcome, defined as live birth and full term. **Results:** a total of 84 SLE patients were enrolled in this study with 109 pregnancies after SLE diagnosis. The median age of subjects at the time of pregnancy was 28 (25-32) years old. Poor pregnancy outcome comprising 22.9% abortion, 14.7% premature birth, 5.5% stillbirth, 1.8% IUGR and 4.6% neonatal death. There was a significant difference in the number of planned pregnancy ($P=0.011$) between groups with poor and good outcome. Clinical variables significantly associated with poor pregnancy outcome were lupus nephritis ($OR = 4.813$, 95% CI 1.709 – 13.557, $P = 0.003$) and neuropsychiatric SLE ($OR = 5.045$, 95% CI 1.278 – 19.920, $P = 0.021$). **Conclusion:** the pregnancy in SLE patient should be planned to have better outcome. Lupus nephritis and neuropsychiatric (NP) SLE were risk factors for poor pregnancy outcome in SLE patient.

Keywords: systemic lupus erythematosus; pregnancy; poor outcome.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease which commonly occurs during childbearing age.¹⁻⁵ Improved treatment in SLE carried better quality of life and allowed pregnancies in SLE patient, yet the pregnancy outcome is still unfavorable. Pregnancy in women with SLE have a higher maternal and fetal risk compared with pregnancy in healthy women.⁶⁻⁸ Maternal complications include lupus flare, hypertension, nephritis, preeclampsia, and eclampsia, while poor pregnancy outcomes include preterm delivery, pregnancy loss, and intra-uterine growth restriction (IUGR).^{9,10} The predictors of adverse pregnancy outcome include maternal age above 35 years old, active maternal disease, nephritis, proteinuria, hypertension, thrombocytopenia, and presence of anti-phospholipid antibodies, especially lupus anticoagulant.^{6,11,12} Clowse ME et al.¹¹ study showed that pregnancy loss was increased 2.6 and 3.3 times in first-trimester women with proteinuria and thrombocytopenia consecutively. High-activity lupus led to a 6-fold increase in fetal loss.¹³ In a pregnant SLE patient, renal involvement known as lupus nephritis is a common feature. The rate of pregnancy loss in patients with active nephritis was reported to be as high as 12 to 38%.¹⁴

Disease activity at the time of conception is an indicator of pregnancy outcomes, and high activity leads to poor outcomes.⁶ Improving

pregnancy outcome in SLE patients could be achieved with good pregnancy plan. Consequently, an awareness of risk factors for poor pregnancy outcome is important. The purpose of this study is to describe pregnancy outcome and determine the risk factors associated with poor pregnancy outcome in SLE.

METHODS

A retrospective case-control study was conducted by retrieving complete medical records of female SLE patients who have been registered in Dr. Hasan Sadikin General Hospital Bandung lupus registry from September 2016 to January 2018. We conducted this study from January 2018 to March 2018. Minimal sample size was calculated using rule of thumb method for five variable risk factors analysis. Subjects in case group were collected by consecutive sampling method within certain time duration, and subjects in control group were matched to the case group based on age at pregnancy, SLE duration, gravidity and parity status. These SLE patients fulfilled at least four of eleven criteria for the classification of SLE from the 1997 American College of Rheumatology (ACR) revised criteria for the classification of SLE.¹⁵ SLE patients who once had pregnancy after SLE diagnosis were enrolled in this study. Patients with incomplete data were excluded. Variable recorded data included the patients' age at SLE diagnosis, the patients' age at pregnancy, SLE disease

duration, and the frequency of pregnancy after SLE diagnosis. These variables were matched to find the difference between groups with poor and good outcome. A poor pregnancy outcome group was defined as pregnancies with abortion (loss of fetal <20 weeks), premature birth (termination of pregnancy with a live birth between weeks 21 and 37)¹⁶, stillbirth (a fetal death that occurs during pregnancy ≥ 20 weeks)¹⁷, intrauterine growth restriction/ IUGR (estimated fetal weight that is less than the 10th percentile for gestational age)¹⁸, and neonatal death. Good pregnancy outcome group was pregnancies with live birth and full-term birth (termination of pregnancy with a live birth between 38 and 42 weeks)¹⁹ in SLE patients. Furthermore, several complications of SLE consisting of lupus nephritis, hypertension (based on European Society of Hypertension/ European Society of Cardiology guidelines)²⁰, thrombocytopenia (platelet levels below 105 cells/uL for two times, unrelated to drugs usage), and neuropsychiatric SLE (NPSLE) (based on ACR neuropsychiatric SLE nomenclature)²¹ were also evaluated for their effects to pregnancy outcome. Lupus nephritis is defined based on WHO lupus nephritis criteria, class III-V.²² Furthermore, planned pregnancy is defined as pregnancy in minimum of six months remission of SLE disease activity and medically monitored at least monthly.²³

Data were analyzed with STATA 14.0 statistical software. Descriptive analyses included mean (SD)/median (Q1-Q3) for continuous numerical outcomes and percentage frequency distribution for categorical data. Homogeneity of baseline pregnancy characteristics between case and control groups such as age at pregnancy, SLE duration, planned pregnancy, multigravida, and multipara were evaluated using Mann–Whitney U and Chi-square tests. Maternal complication characteristics were compared their occurrence between two groups using Chi-square and Fisher's exact tests. All P-values <0.05 were considered statistically significant. Multivariate analysis was performed included five variables (maternal age, lupus nephritis, hypertension, thrombocytopenia, neuropsychiatric SLE) with P-values <0.25 in bivariate analysis. We considered a higher P-value because a traditional

levels (0.05) can fail in identifying variables known to be important.²⁴ Multivariate analysis was performed with logistic regression analysis and backward stepwise process. Odds ratios (OR) >1, falling within the 95% confidence interval were significant correlates. All P-values <0.05 were considered statistically significant.

This is a part of the lupus registry study at Dr. Hasan Sadikin General Hospital Bandung, which has been approved by the Institutional ethic committee on January 2nd, 2018, reference number 01/UN6.C.10/PN/2018. Written informed consent was obtained from each participant in the lupus registry.

RESULTS

A total of 84 SLE patients evaluated in this study with 109 pregnancies after SLE diagnosis. The median age of subjects at the time of pregnancy was 28 (25-32) years old. Twenty (23.8%) of subjects had low levels of education (below or equal junior high school).²⁵ Maternal death was one of the complications of pregnancy;

Table 1. General characteristics of subjects

Variables	n (%)
Age at SLE diagnosis (years), n=84, Mean (SD)	26 (6)
Low levels of education	20 (23.8)
Multigravida	31 (36.9)
Multipara	22 (26.2)
Amount of pregnancy after diagnosis	
- 1	63 (75.0)
- 2	17 (20.2)
- 3	3 (3.6)
- 4	1 (1.2)
Maternal death	2 (2.4)
Poor pregnancy outcome (n=109)	
- Spontaneous abortion	19 (17.4)
- Induced abortion	6 (5.5)
- Premature birth (20 -37 Weeks)	16 (14.7)
- Stillbirth	6 (5.5)
- Intrauterine growth restriction (IUGR)	1 (0.9)
- Neonatal death	4 (3.7)
- Full term birth (38-42 weeks)	0 (0.0)
- Stillbirth	0 (0.0)
- Intrauterine growth restriction (IUGR)	1 (0.9)
- Neonatal death	1 (0.9)
Full term and live birth	55 (50.5)

our study showed 2 (2.4%) mothers died after delivering their babies due to active lupus disease and concomitant infection. (**Table 1**)

Abortion (22.9%) was the most common adverse outcome of pregnancy, including induced abortion (5.5%) in case of blighted ovum, missed abortion, mother's life threatening condition and spontaneous abortion (17.4%), followed by premature birth (14.7%) (**Table 1**). Only 21.1% pregnancies were planned before conception, with 73.9% of planned pregnancies leading to good pregnancy outcome. There was a significant difference between the number of planned pregnancy ($P= 0.011$) in poor outcome and control group (**Table 2**).

Multivariate analysis of independent factors associated with poor pregnancy outcome was done by using logistic regression analysis. The effects of lupus nephritis, hypertension, thrombocytopenia, and neuropsychiatric SLE (predictor variables with P -value <0.25 in bivariate analysis) to pregnancy outcome were examined with multivariate analysis. Lupus nephritis (OR = 4.813, 95% CI 1.709 – 13.557, $P = 0.003$) and neuropsychiatric SLE (OR = 5.045, 95% CI 1.278 – 19.920, $P = 0.021$) were predictors of poor outcome in SLE patients (**Table 3**).

Based on multivariate logistic regression analysis, the probability of poor pregnancy outcome in patients with lupus nephritis and

Table 2. Baseline characteristic comparison of pregnancy outcome in SLE patients

	All pregnancies (n=109)	Poor outcome group (n=54)	Control group (n=55)	P-value
Age at pregnancy (years)				
Median (Q1 - Q3)	28 (25-32)	28 (24 - 33)	28 (26 - 31)	0.721 ^a
SLE duration (months)				
Median (Q1- Q3)	30 (10-66)	24 (10 – 50)	35 (10 – 73)	0.243 ^a
Maternal age >35 years, n (%)	13 (11.9)	8 (14.8)	5 (9.1)	0.357 ^b
Multigravida, n (%)	33 (30.2)	19 (35.2)	14 (25.4)	0.269 ^b
Multipara, n (%)	27 (24.7)	13 (24.1)	14 (25.4)	0.867 ^b
Planned pregnancy, n (%)	23 (21.1)	6 (11.1)	17 (30.9)	0.011 ^{b*}
Maternal complication				
- Rash, n (%)	20 (18.3)	10 (18.5)	10 (18.2)	0.964 ^b
- Arthritis, n (%)	34 (31.2)	15 (27.8)	19 (34.5)	0.446 ^b
- Preeclampsia, n (%)	17 (15.6)	8 (14.8)	9 (16.3)	0.824 ^b
- Lupus nephritis, n (%)	25 (22.9)	19 (35.2)	6 (10.9)	0.003 ^{b*}
- Hypertension, n (%)	18 (16.5)	14 (25.9)	4 (7.3)	0.010 ^{c*}
- Thrombocytopenia, n (%)	15 (13.7)	11 (20.4)	4 (7.3)	0.056 ^c
- Neuropsychiatric SLE, n (%)	14 (12.8)	11 (20.4)	3 (5.4)	0.024 ^{c*}

* P -value <0.05 . Data were analyzed with ^aMann Whitney –U test, ^bChi-square test, ^cFisher's exact test

Table 3. Multivariate logistic regression analysis of risk factors for poor pregnancy outcome in SLE patients

Risk factors	Univariate Logistic Regression		Multivariate Logistic Regression	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Lupus nephritis	4.433 (1.606–12.253)	0.004*	4.813 (1.709– 13.557)	0.003*
Hypertension	4.462 (1.363–14.607)	0.013*		
Thrombocytopenia	3.262 (0.969–10.984)	0.056		
Neuropsychiatric SLE	4.434 (1.162–16.917)	0.029*	5.045 (1.278 – 19.920)	0.021*

NPSLE is 0.934. However, if a patient has only one of risk factors; lupus nephritis or NPSLE, the probabilities are 0.736 and 0.745 respectively (**Figure 1**).

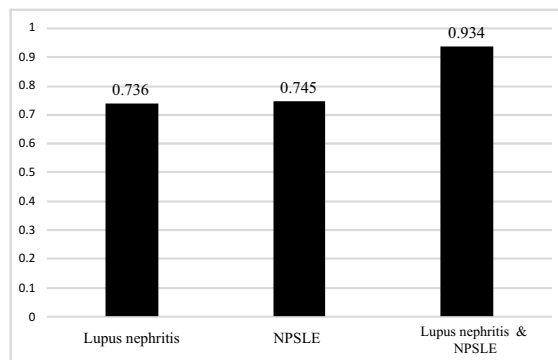


Figure 1. Risk factor probability for poor pregnancy outcome

DISCUSSION

Our subject's age characteristic was similar as several studies in China, Thailand, South Korea and Saudi Arabia but with shorter SLE disease duration.²⁶⁻²⁹ This disease duration difference might carry different clinical presentation and pregnancy outcome.

We demonstrated significant difference of the number of planned pregnancy in pregnancy outcome; with 73.9% of planned pregnancies leading to good pregnancy outcome. The timing of conception is an important aspect of pregnancy outcome. Kwok et al.³⁰ found that a history of nephritis or active lupus disease in SLE patients six months before conception predicts adverse fetal outcomes. Contrary to unplanned pregnancies, fetal survival rate could reach 87.9% in planned pregnancies.²³ Another observational study which included 385 pregnant lupus patients with inactive or mild/moderate disease at conception, demonstrated uncomplicated pregnancies in 81% of subjects.³¹

Immunological adaptations in the pregnant setting of SLE patients lead to high risk of adverse pregnancy outcomes in both the mother and the baby.³² Al Arfaj et al.²⁸ found that live births were significantly fewer (70.2% vs. 85.7%) and more frequently to end in fetal deaths (29.7% vs. 14.2%), and preterm births (26.7% vs. 5.8%) in pregnancies occurring after SLE onset than in pregnancies occurring before SLE onset.

Maternal Outcome

SLE flare is commonly induced by pregnancy in SLE patients. In this study, the most common maternal complications were arthritis (31.2%) and lupus nephritis (22.9%), followed by rash (18.3%), hypertension (16.5%), preeclampsia (15.6%), thrombocytopenia (13.7%), and neuropsychiatric SLE (12.8%). Maternal death occurred in 2.4% of SLE patients. Similarly, a meta-analysis of 37 studies reported the most frequent maternal complications, including lupus flare (25.6%), hypertension (16.3%), nephritis (16.1%), and pre-eclampsia (7.6%) with severe complications (eclampsia, stroke, and maternal death), were observed in 1% of subjects.⁹ In Thailand, Foocharoen et al.²⁹ demonstrated that lupus nephritis, hemolytic anemia, cutaneous rash, and arthritis were the most common manifestations during pregnancy.

Pregnancy Outcome

In this study, the adverse pregnancy outcome included abortion (22.9%), premature birth (14.7%), stillbirth (5.5%), IUGR (1.8%), and neonatal death (4.6%). Compared with previous studies, we have higher abortion (21.9%), stillbirth (3.6%), neonatal death (2.5%), and lower premature birth (39.4%) and intrauterine growth retardation (12.7%).⁹ Another studies even showed 10 to 30 percent of pregnancies in women with SLE are complicated by fetal growth restriction.⁶ The poor pregnancy outcome in our center might be caused by several conditions. Firstly, our center was a tertiary hospital, dealing with more complicated cases. Secondly, there was a high number of unplanned pregnancy (78.9%). Pregnancies should be delayed until the disease has been in remission for 6 months.³⁰

Regression analysis showed that lupus nephritis and neuropsychiatric SLE were two predictors of poor pregnancy outcome in this study. Lupus nephritis might cause microcirculation impairment of uteroplacental vessels.³³ Nephritis history is known to have been associated with pre-eclampsia.⁹ Pregnancies in active lupus nephritis were associated with higher rates of maternal complications (57% vs. 11%) and fetal loss (35% vs 9%) compared those without renal involvement.¹² Women with lupus nephritis were reported to have 39.4%

rates of premature birth.⁹ Furthermore, patients with neuropsychiatric SLE had 5.0 times higher risk of poor pregnancy outcome. They had a higher rate of prematurity and preeclampsia compared with patients without neuropsychiatric disease.³⁴ El-Sayed et al.³⁵ also found extreme prematurity and neonatal death in the central nervous system (CNS) of Lupus patient. It was found an association of neuropsychiatric with antiphospholipid syndrome (APS), especially arterial thrombotic events.³⁶ Antiphospholipid syndrome is associated with an increased risk of preeclampsia, IUGR, and other complications related to uteroplacental insufficiency.³⁷ However, de Jesus et al.³⁴, did not find any association between neuropsychiatric SLE and APS. There was only a limited study with very few subjects on neuropsychiatric SLE with pregnancy. One study even found that when other concomitant risk factors are excluded, the pregnancy outcome becomes more favorable.³⁴

Findings from this study suggest that patients with a history of hypertension have an increased risk of poor pregnancy outcome although the association was not significant in multivariable analysis. Consistent with previous study, hypertension increases the risk of premature deliveries and IUGR 15.7 and 37.7 times respectively.²⁸ Hypertension in pregnancy was found to be associated with prematurity and IUGR by impairing uteroplacental perfusion.^{28,38}

However, thrombocytopenia did not significantly cause poor pregnancy outcome. This result is contrary to two studies in Chinese women which found that the rate of thrombocytopenia significantly increased in patients with fetal loss.^{39,40} The difference in thrombocytopenia definition might explain this finding. It could be noted that these predictor factors might not cause poor pregnancy outcome directly but they were only representation of SLE disease severity.

This was the first study in Indonesia evaluating risk factors and their probabilities for poor pregnancy outcome in SLE patients. There were several limitations in this study. We did not include some risk factors, such as SLE disease activity, antiphospholipid syndrome, history of thrombosis and anti-Ro/SSA antibodies due to data unavailability. The diagnosis of

lupus nephritis in this study was not based on histopathologic examination due to the fact that none of the patients performed kidney biopsy. The effect of SLE medication to pregnancy outcome was also not evaluated. Finally, this study emphasized the importance of the right conception timing to optimize pregnancy. In order to be successful in this action, the guideline for SLE pregnancy planning and termination should be routinely implemented.

CONCLUSION

The pregnancy in SLE patient should be planned to have better outcome. Lupus nephritis and neuropsychiatric SLE were risk factors for poor pregnancy outcome in SLE patient.

CONFLICT OF INTEREST

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