Comparison of Maternal and Perinatal Outcomes of Pregnancy with Systemic Lupus Erythematosus in Planned Referrals Compared to Emergency Referrals Based on the Maternal Fetal Triage Index at Dr. Kariadi General Hospital, Semarang, Indonesia

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A B S T R A C T

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease that attacks the skin and the musculoskeletal, kidney, neuropsychiatric, hematological, cardiovascular, pulmonary, and reproductive systems. In pregnancies with SLE, early referral to the hospital with the involvement of obstetricians and rheumatologists, and other specialists as needed, as well as individual management plans, regular reviews, and early recognition of flares and complications, are important. This study aimed to determine the differences in maternal and perinatal outcomes referred by planned referrals compared to emergency referrals, especially in pregnant patients with SLE. **Methods:** This study was an analytic observational study with a retrospective cohort approach. A total of 40 subjects participated in this study. Data analysis using SPSS software was carried out univariate and bivariate to examine the relationship between types of referrals and maternal and perinatal outcomes. **Results:** There were significant differences between the types of emergency referrals and planned referrals in the variable incidence of preeclampsia and SLE exacerbations. There were no significant differences between the types of emergency referrals and planned referrals on the variable incidence of lupus nephritis, maternal death, premature delivery, fetal growth restriction, fetal death, and the incidence of neonatal lupus syndrome. **Conclusion:** The incidence of severe preeclampsia and SLE exacerbation was lower in planned referrals compared to emergency referrals in pregnant patients with SLE at Dr. Kariadi General Hospital, Semarang, Indonesia.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that attacks the skin and the musculoskeletal, kidney, neuropsychiatric, hematological, cardiovascular, pulmonary, and reproductive systems.[1] The etiopathology of SLE is not known with certainty but is thought to be due to the involvement of genetic and environmental variations that interact in a complex and multifactorial manner.[2] The annual incidence of this disease is around 4-35 cases per 100,000 people in a year, and most are found in childbearing age, with a peak incidence between the ages of 15 and 40 years, with a female: male ratio of 9 : 1.[3,4] The incidence of SLE in pregnant women around between 1:660 to 1:2.952, which can

increase the morbidity and mortality significantly in the fetus and mother.[4]

In pregnancies with SLE, early referral to the hospital with the involvement of obstetricians and rheumatologists, and other specialists as needed, as well as individual management plans, regular reviews, and early recognition of flares and complications, are important. In maternal referral services, there are two patterns of referral, namely planned referral by preparing and planning referrals to the hospital in advance for mothers who are at high risk, while the second pattern is a timely referral for mothers with emergencies-obstetrics. Emergency referrals that are not carried out properly will increase the risk of morbidity and mortality, and the factors that cause poor referrals are the referring health workers do not implement referrals in accordance with emergency referral procedures, such as not educating patients before being referred, not contacting the destination hospital for acceptance readiness. Patient transportation that is used mostly does not use ambulances but private cars, so it takes a long time to prepare a vehicle to take the patient to the hospital. Referrers do not bring the tools and medicines needed during the trip, and referrers do not fill out a complete referral letter.[5-8] This study aims to determine the difference in outcomes for maternal and perinatal referrals by planned referrals compared to emergency referrals, especially in pregnant patients with SLE.

2. Methods

This study was an analytic observational study with a retrospective cohort approach. This study uses secondary data sourced from medical records. A total of 20 subjects in the emergency referral group and 20 subjects in the planned referral group were enrolled in this study. The inclusion criteria included pregnant women of 22 weeks gestation or more with SLE who were treated and gave birth at Dr. Kariadi General Hospital, Semarang, Indonesia, in 2016-2021. This study was approved by the medical and health research ethics committee at Dr. Kariadi General Hospital, Semarang, Indonesia (No.1282/EC/KEPK-RSDK/2022).

The test variables in this study were the type of referral and maternal and perinatal outcomes. Types of referrals are grouped into 2, namely: emergency referrals are pregnant women with SLE who are referred or come alone to the hospital through the polyclinic or emergency unit in obstetric emergencies based on the Maternal Fetal Triage Index priority 1-3, and planned referrals are pregnant women with SLE who are referred or come alone to the hospital through the polyclinic or emergency unit in a stable condition based on the Maternal Fetal Triage Index priority 4-5. Maternal outcomes are outcomes in pregnant women with SLE consisting of severe preeclampsia, SLE exacerbations, Lupus nephritis, and maternal death. Perinatal outcomes are outcomes at 22 weeks to 7 days of gestation from mothers with SLE, which consist of premature birth, neonatal lupus syndrome, IUGR, and fetal death in utero. Data analysis was performed with the help of SPSS software version 25. Univariate analysis was performed to present a frequency distribution table for each test variable. Bivariate analysis was carried out to determine the relationship between the test variables with a p-value <0.05.

3. Results

Table 1 shows the age of the mothers in the emergency referral group obtained an average of 28.55 years with a standard deviation of 5.83 years. The median value was 28 years, with the youngest age being 23 years and the oldest being 41 years. There were 7 subjects in the age range of 17-25 years (35%), 10 subjects in the age range of 26-35 years (55%), and 3 subjects in the age range of 36-45 years (10%). In the planned referral group, the mean was 29.57 years, with a standard deviation of 4.11 years. The median was 29 years, with the youngest age being 24 years and the oldest being 36 years. There were 7 subjects in the age range of 17-25 years (35%), 11 subjects in the age range of 26-35 years (55%), and 2 subjects in the age range of 36-45 years (10%). In planned

referrals and emergency referrals, pregnancies with SLE were mostly in the age range of 26-35 years, namely 55% and 50%. There was no significant difference (p=0.521) in maternal age between the planned referral and emergency referral groups. Maternal body mass index in the emergency referral group obtained an average of 27.41 kg/m² with a standard deviation of 5.37 kg/m², the median value was 27.62 kg/m² with the smallest value being 14 kg/m², and the largest value is 36 kg/m². There were 4 normoweight subjects (20%), 9 overweight subjects (45%), and 7 obese subjects (35%). In the planned reference group, the mean was 27.04 kg/m² with a standard deviation of 5.06 kg/m². The median value was 29.20 kg/m², with the smallest value being 20 kg/m² and the largest value being 34 kg/m². There were 8 normoweight subjects (40%), 6 overweight subjects (30%), and 6 obese subjects (30%). There was no significant difference (p=0.267) in maternal body mass index between the planned referral and emergency referral groups. Gestational age in the emergency referral group was found to be an average of 29.55 weeks with a standard deviation of 5.61 weeks. The median value was 31 weeks, with the youngest being 20 weeks and the oldest being 37 weeks. In the planned referral group, the mean was 35.71 weeks with a standard deviation of 1.49 weeks, and the median was 36 weeks, with the youngest being 34 weeks and the oldest being 38 weeks. There was a significant difference (p=0.002) in gestational age between the planned referral and emergency referral groups. Gravida, in the emergency referral group, obtained an average of 2.09 with a standard deviation of 1.13, a median value of 2 with the smallest value of 1, and the largest value of 4. There were 12 subjects with a history of gravida 1-2 (60%), 5 subjects with a history of gravida 3 -4 (25%), and 3 subjects with a history of gravida 5-6 (5%). In the planned referral group, the mean was 2.14 with a standard deviation of 1.77, and the median value was 2, with the smallest value being 1 and the largest value being 6. There were 16 subjects with a history of gravida 1-2 (80%), 2 subjects with a history of gravida 3-4 (10%), and 2

subjects with a history of gravida 5-6 (10%). There was no significant difference (p=0.409) in the history of gravida between the planned and emergency referral groups. Parity in the emergency referral group obtained an average of 1 with a standard deviation of 1, a median value of 1 with the smallest value of 0, and the largest value of 3. There were 7 subjects with a history of parity 0 (35%), 7 subjects with a history of parity 1 (35%), 5 subjects with a history of parity 2 (25%), and 1 subject with a history of parity 3 (5%). In the planned referral group, the mean was 0.71, with a standard deviation of 0.75. The median value was 1, with the smallest value 0 and the largest value 2. There were 10 subjects with a history of parity 0 (80%), 8 subjects with a history of parity 1 (40%), 1 subject with a history of parity 2 (5%), and 1 subject with a history of parity 3 (5%). There was no significant difference (p=0.386) in historical parity between the planned and emergency referral groups. History of abortion in the emergency referral group obtained an average of 0.09 with a standard deviation of 0.30, a median value of 0 with the smallest value of 0, and the largest value of 1. There were 14 subjects with a history of abortion 0 (70%), 2 subjects with a history of abortion 1 (10%), 4 subjects with a history of abortion 2 (20%), and no subjects with a history of abortion 3 (0%). In the planned referral group, the mean was 0.43, with a standard deviation of 1.13. The median value was 0, with the smallest value being 0 and the largest value being 3. There were 16 subjects with a history of 0 abortion (80%), 3 subjects with a history of 1 abortion (15%), there were no subjects with a history of 2 abortions (0%), and 1 subject with a history of 3 abortions (5%). There was no significant difference (p=0.148) in the history of abortion between the planned and emergency referral groups. Antenatal care at specialist doctors in the emergency referral group obtained an average of 3.18 with a standard deviation of 1.60, a median value of 3 with the smallest value of 1, and the largest value of 6. There were 4 subjects with a history of ANC from specialists 0 times (20%), 5 subjects with a history of ANC from a specialist 1-2 times (25%), 8 subjects with a history of

ANC from a specialist 3-4 times (40%), 3 subjects with a history of ANC from a specialist 5-6 times (15%) and there were no subjects with a history of specialist ANC 7-8 times (0%). In the planned referral group, the mean was 5.00 with a standard deviation of 1.63, the median value was 5, with the smallest value being 3 and the largest value being 8. There was 1 subject with a history of ANC from a specialist 0 times (5%), 5 subjects with a history of ANC from a doctor specialist 1-2 times (25%), 5 subjects with a history of ANC specialist doctor 3-4 times (25%), 7 subjects with a history of ANC specialist doctor 5-6 times (35%) and 2 subjects with a history of ANC specialist doctor 7-8 times (10%). There was a significant difference (p=0.030) in the history of antenatal care at specialist doctors between the planned referral and emergency referral groups. Antenatal care in midwives in the emergency referral group obtained an average of 1.55 with a standard deviation of 1.03, a median value of 2 with the smallest value of 0, and the largest value of 3. There were 5 subjects with a history of 0 times midwifery ANC (25%), 13 subjects with a history of 1-2 times (65%) of the midwife's ANC, 2 subjects with a history of the midwife's ANC of 3-4 times (10%), and no subjects with a history of the midwife's ANC of 5-6 times (0%). In the planned referral group, the mean was 2.71, with a standard deviation of 2.28. The median value was 3, with the smallest value 0 and the largest value 6. There were 5 subjects with a history of 0 times a midwife's ANC (25%), 5 subjects with a history of a midwife's ANC 1-2 times (25%), 8 subjects with a history of midwife ANC 3-4 times (40%), and 2 subjects with a history of midwife ANC 5-6 times (10%). There was a significant difference (p=0.048) in the history of antenatal care at the midwife between the planned referral and emergency referral groups. Long suffered from SLE, in the emergency referral group obtained an average of 1.27 years with a standard deviation of 2.08 years, the median value was 0 years with the smallest value being 0 years and the largest value being 8 years. In the planned referral group, the mean was 2.60 years with a standard deviation of 2.83 years, and the median value was 2

years, with the smallest value being 0 years and the largest value being 9 years. There was no significant difference (p=0.149) in the duration of SLE between the planned referral and emergency referral groups. Origin of referral, in the emergency referral group, there were 7 subjects who came alone (35%) and 13 subjects who were referred from the hospital (65%). In the planned referral group, there were 4 subjects who came alone (20%) and 16 referral subjects from the hospital (80%). There was no significant difference (p=0.480) in the origin of referrals between the planned and emergency referral groups. Funding in the emergency referral group, there were 5 subjects using JKN PBI (25%) and 15 subjects using JKN non-PBI (75%). In the planned referral group, 7 subjects used JKN PBI (35%), and 13 subjects used JKN non-PBI (65%). There was no significant difference (p=0.731) in the type of financing in the planned referral and emergency referral groups.

Based on Table 2, in the emergency referral group, there were 12 subjects with severe preeclampsia (60%) and 8 subjects without severe preeclampsia (40%). In the planned referral group, there were no subjects with severe preeclampsia. There was a significant difference (p<0.001) in cases of severe preeclampsia between the planned and emergency referral groups. Subjects with severe preeclampsia are at 3.5 times greater risk for an emergency referral than subjects without severe preeclampsia. In the emergency referral group, there were 10 subjects with SLE exacerbations (50%) and 10 subjects without SLE exacerbations (50%). In the planned referral group, there were 2 subjects with SLE exacerbations (10%) and 18 subjects without SLE exacerbations (90%). There was a significant difference (p=0.014) in cases of SLE exacerbations between the planned referral and emergency referral groups. Subjects with SLE exacerbations are at risk 2.33 times greater for experiencing emergency referral than subjects without SLE exacerbations. In the emergency referral group, there were 8 subjects with lupus nephritis (40%) and 12 subjects without lupus nephritis (60%). In the planned referral group, there were 4 subjects with lupus nephritis (20%) and 16

subjects without lupus nephritis (80%). There was no significant difference (p=0.301) in cases of lupus nephritis between the planned referral and emergency referral groups. In the emergency referral group, 4 out of 20 mothers died (20%). In the planned referral group, 1 in 20 mothers died (5%). There was no significant difference (p=0.342) in cases of maternal death between the planned referral and emergency referral groups.

Table 1. Demographic data of study subjects.

Variable	Emergency referral			Planned referral			p
	n	Mean ± SD	Median (min-max)	n	Mean ± SD	Median (min-max)	
Maternal age, years		28.55 ± 5.83	28 (23-41)		29.57 ± 4.11	29 (24-36)	0.521[†]
17-25	7 (35%)			7 (35%)			
26-35	10 (50%)			11 (55%)			
36-45	3 (15%)			2 (10%)			
Maternal body mass index, kg/m^2		27.41 ± 5.37	27.62 (14-36)		27.04 ± 5.06	29.20 (20-34)	0.267[§]
Normoweight	4 (20%)			8 (40%)			
Overweight	9 (45%)			6 (30%)			
Obesity	7 35%)			6 (30%)			
Gestational age, weeks		29.55 ± 5.61	31 (20-37)		35.71 ± 1.49	36 (34-38)	0.002[†]
Gravida		2.09 ± 1.13	2 (1-4)		2.14 ± 1.77	2 (1-6)	0.409[§]
1-2	12 (60%)			16 (80%)			
3-4	5 (25%)			2 (10%)			
5-6	3 (5%)			2 (10%)			
Parity		1.00 ± 1.00	1 (0-3)		0.71 ± 0.75	1 (0-2)	0.386[§]
0	7 (35%)			10 (50%)			
1	7 (35%)			8 (40%)			
2	5 (25%)			1 (5%)			
3	1 (5%)			1 (5%)			
History of abortion		0.09 ± 0.30	0 (0-1)		0.43 ± 1.13	0 (0-3)	0.148[§]
0	14 (70%)			16 (80%)			
1	2 (10%)			3 (15%)			
2	4 (20%)			0 (0%)			
3	0 (0%)			1 (5%)			
Specialist doctor's antenatal care		3.18 ± 1.60	3 (1-6)		5.00 ± 1.63	5 (3-8)	0.030[†]
0	4 (20%)			1 (5%)			
1-2	5 (25 %)			5 (25%)			
3-4	8 (40%)			5 (25%)			
5-6	3 (15%)			7 (35%)			
7-8	0 (0%)			2 (10%)			
Midwife's antenatal care		1.55 ± 1.03	2 (0- 3)		2.71 ± 2.28	3 (0-6)	0.048[†]
0	5 (25%)			5 (25%)			
1-2	13 (65%)			5 (25%)			
3-4	2 (10%			8 (40%)			
5-6	0 (0%)			2 (10%)			
Length of suffering from SLE		1.27 ± 2.08	0 (0 -8)		2.60 ± 2.83	2 (0-9)	0.149[‡]
Origin of referral							0.480[£]
Comes alone	7 (35%)			4 (20%)			
Hospital	13 (65%)			16 (80%)			
Financing							0.731[£]
JKN PBI	5 (25%)			7 (35%)			
JKN non-PBI	15 (75%)			13 (65%)			

[†]Independent T test; [‡]Mann Whitney U; [£]Chi Square; [§]Fisher Exact; *significant p<0.05.

Table 2. The maternal outcome between emergency referral and planned referral.

Variable	Emergency referral	Planned referral	p	RR
Severe preeclampsia			< 0.001£	3.5 (1.94-6.28)
Yes	12 (60%)	0 (0%)		
No	8 (40%)	20 (100%)		
SLE exacerbation			0.014£	2.33 (1.33-4, 07)
Yes	10 (50%)	2 (10%)		
No	10 (50%)	18 (90%)		
Lupus nephritis			0.301£	1.55 (0.86-2.79)
Yes	8 (40%)	4 (20%)		
No	12 (60%)	16 (80%)		
Maternal mortality			0.342§	1.75 (0.99-3.08)
Yes	4 (20%)	1 (5%)		
No	16 (80%)	19 (95%)		

£Chi Square; §Fisher Exact; *significant p<0.05.

Table 3. The perinatal outcome between emergency referral and planned referral.

Variable	Emergency referral	Planned referral	p	RR
Premature birth			0.191£	1.80 (0, 82-3,94)
Yes	15 (75%)	10 (50%)		
No	5 (25%)	10 (50%)		
Neonatal lupus syndrome			1,000§	-
Yes	0 (0%)	0 (0%)		
No	20 (100%)	20 (100%)		
IUGR			1,000£	1.10 (0.59-2.05)
Yes	9 (45%)	8 (40) %		
No	11 (55%)	12 (60%)		
IUFD			1,000§	1.37 (0.57-3.25)
Yes	2 (10%)	1 (5.3%)		
No	18 (90%	19 (94.7%)		

£Chi Square; §Fisher Exact; *significant p<0.05.

Based on Table 3, in the emergency referral group, there were 15 babies with premature births (75%) and 5 babies with full-term births (25%). In the planned referral group, there were 10 babies with premature births (50%) and 10 babies with full-term births (50%). There was no significant difference (p=0.191) in cases of preterm birth between the planned referral and emergency referral groups. In the emergency referral and planned referral groups, there were no infants with neonatal lupus syndrome. There was no significant difference (p=1,000) in cases of neonatal lupus syndrome between the planned referral and emergency referral groups. In the emergency referral group, there were 9 babies with IUGR (45%) and 11 babies without IUGR (55%). In the planned referral group, there were 8 babies with IUGR (40%) and 12 babies without IUGR (60%). There was no significant difference (p=1,000) in cases of IUGR between the planned and emergency referral groups. In the

emergency referral group, there were 2 babies with IUFD (10%) and 18 babies born alive (90%). In the planned referral group, there was 1 baby with IUFD (5.3%) and 19 babies alive (94.7%). There was no significant difference (p=1,000) in cases of IUFD between the planned and emergency referral groups.

4. Discussion

Women with SLE have a 2 to 4-fold increase in pregnancy complications. SLE tends to increase during pregnancy, and the highest exacerbation rates occur in the third trimester. Most exacerbations are mild, with skin and joint disease being the most common manifestations. In addition, pregnancy outcomes are influenced by other factors, including placental dysfunction, antiphospholipid (aPL) antibodies, pre-conceptional SLE activity, the severity of renal involvement, and the occurrence of SLE during pregnancy. The presence of aPL is a predictor

of maternal thrombosis, embryo/fetal loss, and preeclampsia in women with aPL and thrombosis, so it is advisable for SLE patients not to become pregnant. Preeclampsia was diagnosed in 22.5% of women with SLE compared to 7.6% of the general population. Pregnant women with SLE, when compared with normal women, experienced more cesarean delivery (48% vs 21%), maternal death, preeclampsia, preterm labor (36% vs 18%), thrombosis, infection, and haematological complications during pregnancy. Severe kidney, lung, or heart disease is a life-threatening complication of SLE, and patients should avoid pregnancy due to the high risk of maternal and fetal complications in terms of spontaneous abortion (10-35% of cases), prematurity, IUGR (10-66%) and high perinatal mortality rates.

Pregnant women with SLE have worse pregnancy outcomes than normal women. In a nationwide inpatient sample study that included 4000 SLE pregnancies, pregnancies with SLE had a longer hospital stay, increased hypertension, higher rates of IUGR, and higher rates of cesarean sections. In studies using the same database, there was a 3-fold increased risk of preeclampsia, a 20-fold increased maternal mortality, and increased infection and thrombosis rates among SLE patients. More recent data show increased maternal and fetal mortality, although these rates are still higher than in the control population. The incidence of cesarean section and preeclampsia is always higher in SLE pregnancies and does not change significantly over time. In another study, 19% of patients had an adverse pregnancy outcome, including loss of the fetus after 12 weeks, neonatal death, preterm birth, and small gestation. Early predictors included the presence of anticoagulants (OR 8.32, 95% CI 3.59-19.26), use of antihypertensives (OR 7.05, 95% CI: 3.05-16.31), thrombocytopenia (OR 1.33 .95% CI 1.09–1.63), maternal exacerbations, higher disease activity and lower C3 elevation later in life. Associated with an increased risk of preeclampsia (OR 5.33 compared to control population, OR 3.38 compared to inactive disease) and preterm birth (OR 8.66 compared to control population, OR 3.36 compared to inactive disease). A study of maternal and fetal outcomes spanning 3 decades found that patients with active lupus nephritis compared with those in remission had a higher incidence of maternal complications (57% vs. 11%, p < 0.001). Women with active nephritis were more likely to go into preterm labor (median 34 weeks vs 40 weeks, p = 0.002) and miscarry (35% vs 9%, p = 0.031).[9-15]

Premature birth rates are also higher among mothers with SLE. Because preterm birth has been shown to be associated with maternal age and hypertensive disorders, after using models controlling for maternal age and hypertensive disorders, maternal SLE was independently associated with preterm birth. Newborns may develop neonatal lupus syndrome, manifesting as skin rashes, congenital heart (atrial-ventricular) block, and abnormally low blood counts, such as leukopenia, anemia, and thrombocytopenia. Neonatal lupus syndrome is caused by anti-Ro/SSA and anti-La/SSB antibodies crossing the placenta, which can have a direct toxic effect on cardiac conduction tissue, disrupting the normal function of the sinuses and atrioventricular nodes by interfering with calcium channels. Neonatal lupus syndrome, although rare, carries significant mortality (24% of cases) and morbidity when the fetal heart is the target organ, and nearly half of the surviving children require repeat examinations in the first year of life. In this study, there were no subjects who gave birth to babies with neonatal lupus syndrome, both in cases of emergency referrals and planned referrals. In one study in 2059, SLE offspring reported higher rates of IUGR problems, preterm birth, and stillbirth. Similarly, another study reported a higher risk of preterm and small birth for gestational-age infants in the SLE cohort. This group also found SLE pregnancies to be more likely to experience preterm labor, particularly in hospitalized patients with a history of lupus nephritis and hypertension. IUGR is associated with hypertension and disease exacerbations. Fetal mortality in pregnancies with SLE reaches 43%. This rate will decrease to 17% by 2022.

In a cross-sectional study of 356 pregnancies with SLE, SLE pregnancies were twice as likely to end in fetal death as non-SLE pregnancies. Another study of 148 SLE pregnancies compared with 78,905 non-SLE found that SLE pregnancies had a higher stillbirth rate (OR 4.84 [CI, 1.72,11.08]) and were associated with the severe maternal disease. Risk factors for abortion include the presence of antiphospholipid antibodies (aPL), lupus nephritis, renal insufficiency, and increased SLE activity in the 6 months before or during pregnancy.[16-20]

5. Conclusion

The incidence of severe preeclampsia and SLE exacerbation is lower in planned referrals compared to emergency referrals in pregnant patients with SLE at Dr. Kariadi General Hospital, Semarang, Indonesia.

6. References

1. Lam NC, Ghetu MV, Bieniek ML. Systemic lupus erythematosus: primary care approach to diagnosis and management. American Family Physician. 2016; 94(4): 284-94.

2. Zamani B, Shayestehpour M, Esfahanian F, Akbari H. The study of factors associated with pregnancy outcomes in patients with systemic lupus erythematosus. BMC Research Notes. 2020; 13(1): 1-6.

3. Pastore DE, Costa ML, Surita FG. Systemic lupus erythematosus and pregnancy: the challenge of improving antenatal care and outcomes. Lupus. 2019; 28(12): 1417-26.

4. Hahn B, McMahon M, Wilkinson A, et al. American college of rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012; 64(6): 797–808.

5. Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. Rheumatic Disease Clinics. 2017; 43(2): 215-26.

6. Knight CL, Nelson-Piercy C. Management of systemic lupus erythematosus during pregnancy: challenges and solutions. Open Access Rheumatology: Research and Reviews. 2017; 9: 37.

7. Yamamoto Y, Aoki S. Systemic lupus erythematosus: strategies to improve pregnancy outcomes. International Journal of Women's Health. 2016; 8: 265.

8. Saha MM, Biswas SC, Ghosh A, Tiwari S. A prospective study to evaluate pregnancy outcomes in patients with systemic lupus erythematosus. Journal of South Asian Federation of Obstetrics and Gynecology. 2018; 10(1): 45-8.

9. Pons-Estel GJ, Ugarte-Gil MF, Alarcón GS. Epidemiology of systemic lupus erythematosus. Expert Rev Clin Immunol. 2017; 13(8): 799-814.

10. Choi J, Kim ST, Craft J. The pathogenesis of systemic lupus erythematosus—an update. Current Opinion in Immunology. 2012; 24(6): 651-7.

11. Bertsias G, Cervera R, Boumpas DT. Systemic lupus erythematosus: pathogenesis and clinical features. EULAR Textbook on Rheumatic Diseases. 2012; 5: 476-505.

12. Liu CC, Kao AH, Manzi S, Ahearn JM. Biomarkers in systemic lupus erythematosus: challenges and prospects for the future. Therapeutic Advances in Musculoskeletal Disease. 2013; 5(4): 210-33.

13. Kuhn A, Bonsmann G, Anders HJ, Herzer P, Tenbrock K, et al. The diagnosis and treatment of systemic lupus erythematosus. Deutsches Ärzteblatt International. 2015; 112(25): 423.

14. Karpouzas GA, Kitridou RC. The mother in systemic lupus erythematosus, In: Wallace DJ, Hahn BH. Editors. Dubois' lupus erythematosus. Philadelphia. Lippincott Williams and Wilkins. 2007: 992-1038.

15. Huong D Le T, Wechsler B, Vauthier-Brouzes D, Beauils H, Lefebvre G, et al. Pregnancy in past or present lupus nephritis: a study of 32

pregnancies from a single centre. Ann Rheum Dis. 2001; 60: 599-604.

16. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology. 2017; 56(11): 1945-61.

17. de Jesus GR, Mendoza-Pinto C, de Jesus NR, Dos Santos FC, Klumb EM, Carrasco MG, Levy RA. Understanding and managing pregnancy in patients with lupus. Autoimmune Diseases. 2015; 2015.

18. Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. Journal of Clinical Pathology. 2003; 56(7): 481-90.

19. Bertsias G, Cervera R, Boumpas DT. Systemic lupus erythematosus: pathogenesis and clinical features. EULAR Textbook on Rheumatic Diseases. 2012; 5: 476-505.

20. Maidhof W, Hilas O. Lupus: an overview of the disease and management options. Pharmacy and Therapeutics. 2012; 37(4): 240.