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Original Article

# Prognosis of Neonates in Pregnant Women with Systemic Lupus Erythematosus

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**Purpose:** The effects of maternal systemic lupus erythematosus (SLE) on neonatal prognosis were examined by comparing clinical features of full-term babies born to lupus mothers and age- and parity-matched controls. **Patients and Methods:** From January 2000 to December 2005, 39 singletons were born to 37 SLE women. Excluding 11 cases of prematurity and preeclampsia, 28 full-term neonates formed the lupus group. The control group included 66 full-term babies. The retrospective study examined medical records and compared gestational age, birth weight, days of hospital stay, small for gestational age (SGA) frequency, Apgar scores < 7, and parity. Lupus neonates were tested for anti-nuclear antibody (ANA) and platelet count, and electrocardiogram was performed. **Results:** Average gestational age (38 vs. 39 weeks, $p < 0.05$) and birth weight (2,775 vs. 3,263 g, $p < 0.05$) were significantly different between the SLE and control groups. SGA frequency was higher in the SLE group (25% vs. 4.5%, $p < 0.05$). No significant difference was observed in Apgar score, birth weight, gestational age, SGA frequency, and platelet count between lupus subgroups formed based on anti-dsDNA antibody levels and antiphospholipid antibody status. **Conclusion:** The association of maternal ANAs, antiphospholipid antibodies, and drug history with neonatal prognosis could not be elucidated. However, even in uncomplicated pregnancies, maternal lupus is disadvantageous for gestational age, birth weight, and SGA frequency.

**Key Words:** Lupus erythematosus, systemic, newborn

## INTRODUCTION

Systemic lupus erythematosus (SLE) is an important risk factor for mothers during pregnancy and the puerperal period. Lupus women are thought to experience disease deterioration due to pregnancy, but varying incidence rates have been reported.[1] Maternal lupus is known to influence fetal and neonatal outcomes and is associated with increased incidence of obstetric complications such as stillbirth, abortion, prematurity, intrauterine growth restriction (IUGR), and neonatal complications such as congenital heart block and neonatal lupus.[1-3] In particular, mothers with increased SLE activity, lupus nephritis, hypertension, and who are positive for antiphospholipid and anti-Ro/ SS-A antibodies have relatively poor fetal and neonatal prognosis. However, few studies have investigated the neonatal prognosis in SLE mothers who delivered at full term without obstetrical complications.[1]

Our study focused on the effects of SLE on perinatal outcome by comparing clinical features of full-term neonates born to lupus mothers and normal pregnant women.

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## PATIENTS AND METHODS

### Patients

From January 2000 to December 2005, 37 pregnant women with lupus gave birth at the Kangnam St. Mary's Hospital, The Catholic University of Korea, and 2 women gave birth twice. These women were diagnosed with SLE at the Department of Internal Medicine of the same hospital, and the average duration between diagnosis and delivery was 6.2 years. Of the 39 neonates, 8 born prematurely and 3 born to preeclamptic mothers were excluded, and 28 full-term neonates born between 37 and 41 weeks

of gestation were included in the lupus group. The control group included 66 full-term neonates born to age- and parity-matched pregnant women.

The distribution of pregnant women in the 2 groups was 27 in the lupus group and 66 in the control group. We excluded women with conditions that could influence perinatal prognosis such as premature rupture of membranes (PROM), placental abruption, placenta previa, gestational diabetes, chronic or pregnancy hypertension, and chromosomal abnormalities.

### Methods

This retrospective study investigated medical records of subjects. The lupus and control groups were compared with respect to gestational age, birth weight, days of hospital stay, SGA, Apgar score, and parity. In the lupus group, ANA titers and platelet count were assessed at birth, and electrocardiogram monitoring was performed until discharge. ANA-positive neonates were followed p until conversion to negative was confirmed.

On the other hand, based on the maternal ANA titers prior to delivery, the lupus group was divided into 2 sets of subgroups: (i) cases with anti-dsDNA antibody values greater than 100 IU/mL (10 neonates) and cases with values lower than 100 IU/mL (18) and (ii) cases positive for antiphospholipid autoantibody (6) or negative cases (22). The respective subgroups were compared with respect to 1-min and 5-min Apgar scores less than 7, birth weight, gestational age, SGA frequency, and platelet count.

Antiphospholipid antibody-positive cases were defined as those that were positive for any of the following: anticardiolipin antibody, lupus anticoagulant, or VDRL (the positive VDRL result was a false positive).

### Statistical analysis

SPSS for Windows (ver. 12.0) was used for statistical analysis, Mann-Whitney test for continuous variables, and Fisher's exact test for non-continuous variables.

## RESULTS

### Comparison of maternal demographic data

The mean age of the pregnant women was 31.9 years in the control group and 30.5 years in the lupus group. Among 27 pregnant women of the lupus group (28 neonates), 17 were primiparas and 10 were multiparas. In the control group (66 neonates), 32 women were primiparas and 34 were multiparas. There were no significant differences in age of mothers and ratio of primiparas to multiparas between the 2 groups (Table 1). Regarding the parity of the mothers, there were 12 abortions (48%) and 4 prematurities (16%) among the 25 pregnancies in the lupus group. Among the 75 pregnancies in the control group, there were 32 abortions (42.6%) and 3 prematurities (4%). The incidence of abortion and prematurity was not statistically significantly different between the 2 groups (Table 1).

**Table 1.** Comparison of Perinatal History between Lupus and Control Groups

| | Lupus mothers (n = 27) | Control mothers (n = 66) | *p* value |
|---|---|---|---|
| Age* (yrs) | 30.5 ± 2.9 | 31.9 ± 3.9 | 0.08‡ |
| Primipara to multipara ratio | 17 : 10 | 32 : 34 | 0.25§ |
| Abortion history† | 12 | 32 | 0.63‡ |
| Prematurity history† | 4 | 3 | 0.12‡ |

*Mean ± SD.
†Number.
‡vs. controls by Mann-Whitney test.
§vs. controls by Fisher's exact test.

**Comparison of perinatal outcome between SLE and control groups**

The gender ratio of neonates was 1 : 1.8 in the lupus group (10 males and 18 females) and 1 : 1 in the control group. The average gestational age and birth weight were 38 weeks and 4 days and 2,775 g in the lupus group (28 neonates) and 39 weeks and 5 days and 3,263 g in the control group (66 neonates), respectively, and a significant difference was observed between the 2 groups ($p < 0.05$). The frequency of SGA was 7 cases (25%) in the lupus group and 3 (4.5%) in the control group, and a significant difference was observed between the 2 groups ($p < 0.05$). Thus, compared with the control group, the lupus group had relatively lower birth weight and gestational age and higher SGA frequency (Table 2). There were no significant differences in gender ratio, 1-min and 5-min Apgar scores < 7, and days of hospital stay between the 2 groups.

**Antinuclear antibody and platelet count of neonates**

ANA testing was performed in 17 neonates in the lupus group; 10 neonates were tested positive for anti-dsDNA antibodies at birth and converted to negative at 6 - 12 month after birth. Anti-Ro/SS-A and anti-La/SS-B antibodies were detected in 5 and 3 neonates, respectively (Table 3). Three cases were tested positive for Ro/SS-A and La/SS-B autoantibodies in concomitance.

None of the neonates showed congenital heart block on electrocardiogram at birth and during

**Table 2.** Comparison of Perinatal Outcomes between Lupus and Control Groups

| | Lupus (28 neonates) | Control (66 neonates) | *p* value |
|---|---|---|---|
| Gender (M : F) | 1 : 1.8 | 1 : 1 | 0.260§ |
| Birth weight (g)* | 2,775 ± 360 | 3,263 ± 404 | 0.000‡ |
| Gestational age (wks)* | 38.4 ± 1.0 | 39.5 ± 0.9 | 0.000‡ |
| Hospital stay (d)* | 3.57 ± 3.0 | 2.83 ± 1.8 | 0.461‡ |
| Small for gestational age† | 7 (25%) | 3 (4.5%) | 0.007§ |
| Apgar score < 7 (1 min)† | 2 (7.1%) | 1 (1.5%) | 0.211§ |
| Apgar score < 7 (5 min)† | 1 (3.5%) | 0 (0%) | 0.298§ |

*Mean ± SD.
†Number (%).
‡vs. controls by Mann-Whitney test.
§vs. controls by Fisher's exact test.

**Table 3.** Laboratory Findings of Lupus Group

| | Lupus group (28 neonates) |
|---|---|
| Platelet (/mm$^3$)* | 219,820 ± 63,835 |
| Anti-dsDNA antibody (positive)† | 10 (35.7%) |
| Anti-Ro/SS-A antibody (positive)† | 5 (17.9%) |
| Anti-La/SS-B antibody (positive)† | 3 (10.7%) |
| Anti-dsDNA antibody titer (mother)† | > 100 IU/mL 10 (35.7%)<br>< 100 IU/mL 18 (64.3%) |
| Antiphospholipid antibody (mother, positive‡)† | 6 (21.4%) |

*Mean ± SD.
†Number (%).
‡Lupus anticoagulant (+), anticardiolipin antibody (+), or VDRL (+; the positive VDRL result was a false positive).

**Table 4.** Comparison of Perinatal Outcomes between High- and Low-risk Subgroups (by anti-dsDNA antibody titer) in Lupus Group

| | ≥ 100 IU/mL (10 neonates) | < 100 IU/mL (18 neonates) | *p* value |
|---|---|---|---|
| Birth weight (g)* | 2,641 ± 367 | 2,850 ± 344 | 0.2‡ |
| Gestational age (wks)* | 38.2 ± 0.9 | 38.5 ± 1.1 | 0.4‡ |
| Platelets (/mm$^3$)* | 229,000 ± 60,046 | 218,940 ± 66,836 | 1.0‡ |
| Small for gestational age† | 3 (30.0%) | 4 (22.2%) | 0.6§ |
| Apgar score < 7 (1 min)† | 0 (0.0%) | 2 (11.1%) | 0.5§ |
| Apgar score < 7 (5 min)† | 0 (0.0%) | 1 (5.6%) | 1.0§ |

*Mean ± SD.
†Number (%).
‡vs. controls by Mann-Whitney test.
§vs. controls by Fisher's exact test.

**Table 5.** Comparison of Perinatal Outcomes between aPL-positive and -negative Subgroups in Lupus Group

| | Positive (6 neonates) | Negative (22 neonates) | *p* value |
|---|---|---|---|
| Birth weight (g)* | 2,866 ± 158 | 2,750 ± 397 | 0.3‡ |
| Gestational age (wks)* | 38.8 ± 0.75 | 38.3 ± 1.1 | 0.2‡ |
| Platelets (/mm$^3$)* | 263,170 ± 45,446 | 210,620 ± 64,101 | 0.1‡ |
| Small for gestational age† | 0 (0.0%) | 7 (31.8%) | 0.2§ |
| Apgar score < 7 (1 min)† | 0 (0.0%) | 2 (9.1%) | 1.0§ |
| Apgar score < 7 (5 min)† | 0 (0.0%) | 1 (4.5%) | 1.0§ |

*Mean ± SD.
†Number (%).
‡vs. controls by Mann-Whitney test.
§vs. controls by Fisher's exact test.

the monitoring period or developed neonatal lupus due to ANA transmission from the mother.

Among the pregnant women in the lupus group, thrombocytopenia (platelet count of mother < 100,000/mm$^3$) was observed in 7 women (25.9%) and 2 of their neonates (platelet count of neonate < 150,000/mm$^3$). In all, 5 neonates showed thrombocytopenia (platelet count of neonate < 150,000/mm$^3$), and they recovered within 14 days after birth without any special treatment.

**Perinatal outcome according to lupus activity**

The 2 lupus subgroups based on the maternal anti-dsDNA antibody titers showed no significant differences in 1-minute and 5-minute Apgar scores < 7, birth weight, gestational age, SGA frequency, and platelet count (Table 4). The differences in the clinical manifestations including a history of thrombosis, late-term pregnancy loss, or 3 prior first-trimester miscarriages observed between the 2 subgroups was not significant.

Similarly, the 2 lupus subgroups, based on antiphospholipid autoantibody status, showed no significant differences in 1-minute and 5-minute Apgar scores of the neonates, birth weight, gestational age, SGA frequency, and platelet count (Table 5). Meanwhile, patients with or without antiphospholipidic antibodies (aPL) were provided with similar treatment. In the lupus group, medication history prior to pregnancy included systemic steroids in 25 patients, hydroxychloroquine in 11,

azathioprine in 2, methotrexate in 1 (the neonate did not exhibit any fetal abnormality), and aspirin in 10. In 6 patients with aPL, medication history prior to pregnancy included systemic steroids in 6 patients, hydroxychloroquine in 3, azathioprine in 2, and aspirin in 4. Furthermore, medication history of patients with aPL during pregnancy included systemic steroids in 6 patients and aspirin in 4.

## DISCUSSION

Lupus mothers have a high risk of experiencing spontaneous abortion, stillbirth, prematurity, and IUGR.[1-4] In 1993, Petri et al.[5] examined 481 neonates born to 203 lupus women and the incidence of spontaneous abortion and stillbirth was 21% and prematurity was 12%. These incidence rates were significantly higher than those in healthy pregnant women. In 2000, Georgiou et al.[6] reported that, among the 59 neonates born to 47 lupus mothers, 5% were born prematurely. In our study, 37 lupus women delivered 39 neonates of which 8 (20.5%) were born prematurely. This is a very high rate when compared with the prematurity rate of 0.9% (9 in 1,000 deliveries) reported by the Korea National Statistical Office in 2005. Regarding the parity of the lupus group (28 neonates), there were 12 abortions (48%) and 4 premature deliveries (16%) among a total of 25 pregnancies, whereas there were 32 abortions (42.6%) and 3 premature deliveries (4%) among a total of 75 pregnancies in the control group. Thus, the frequency of prematurity and abortion was higher in the lupus group than the control group, however, a statistically significant difference was not observed. In another Korean report[7] investigating the parity of 91 lupus women from 1990 to 1996, the fetal loss was 19.7% and prematurity rate was 35.6%. The rates observed in the present study were lower, which might be due to the inclusion of lupus mothers with full-term deliveries.

Poor neonatal prognosis has been reported in lupus women with disease deterioration, ANA-positive status, or increased ANA titers.[8,9] However, in our study, a significant difference in neonatal prognosis was not observed between the 2 lupus subgroups based on anti-dsDNA antibody titers $\geq 100$ and $< 100$. This could due to the fact that subjects were restricted to healthy full-term neonates born to mothers without preeclampsia. The presence of aPL in lupus mothers is 30 - 40%,[2] and this is associated with frequent abortion, IUGR, oligohydramnios, preeclampsia, stillbirth, and HELLP syndrome.[1-4,10] In 2003, Moroni et al.[11] reported a strong possibility of lupus mothers positive for aPL or with nephritis losing their fetuses due to factors such as stillbirth and abortion, and the incidence of abortion varied from 30% to 83%. In comparison, in lupus mothers without aPL, the incidence of abortion was 4 - 43%, which was lower than that in mothers positive for these antibodies. However, it has been reported that chances of stillbirth or abortion in mothers positive for aPL could be reduced by aspirin or heparin treatment.10 In our study, among the 28 neonates, maternal aPL were detected in 6 cases (21.4%) and there were only 2 abortions (33.3%). In 22 mothers negative for aPL, 10 (45.4%) had a history of abortion. Thus, our results differ from those reported by Moroni in 2003.11 In addition, a comparison of pregnant women testing positive (6 neonates) and negative (22 neonates) for aPL showed no differences in Apgar scores of neonates, birth weight, gestational age, SGA frequency, and platelet count. However, it appears to be necessary to conduct additional studies with a larger number of subjects.

It has been reported that besides aPL, the presence of ANAs during pregnancy may affect the prognosis of the perinatal period.[12] In particular, anti-Ro/SS-A and anti-La/SS-B antibodies were associated with neonatal lupus[2] and congenital heart block, but, they were not associated with stillbirth, abortion, and prematurity.[13]

Many lupus mothers take medications during pregnancy. Steroids are relatively safe in pregnant women,[2] and it has been reported that fetal mortality and morbidity rates decreased in lupus mothers when treated with steroids.[14] However, Molad et al.[1] have reported in 2005 that not only high lupus activity but also hypoalbuminemia, proteinuria, presence of ANAs, and history of drugs such as steroids and hydroxychloroquine could be risk factors in lupus mothers. In our study, 25 among the 27 lupus women (92.6%) had received systemic steroid treatment, but, it could

not be determined whether this acted as an advantageous factor in maintaining the pregnancy to full term.

In our study, 5 among the 28 lupus neonates showed thrombocytopenia with platelet counts in the range of 83,000 to 149,000/$mm^3$. Platelet count became normal within 2 weeks in most cases, and administration of immunoglobulin or other drugs was not required. Our findings were different from those of other reports[15] in that the problem of thrombocytopenia was not greatly enhanced. This is thought to be due to the inclusion of full-term neonates and low-risk pregnancy subjects without complications such as preeclampsia and prematurity.

In a Korean study on 11 neonates born to 9 SLE women, 9 women had a total of 30 pregnancies among which there were 6 spontaneous abortions (20.0%) and 5 stillbirths (16.7%), and among the neonates, 4 were born prematurely (36.4%) and 2 were SGA (19.2%).[15] From birth, 2 neonates showed thrombocytopenia and leucopenia, and 2 pregnant women positive for lupus anticoagulant and aPL experienced preterm delivery.[15]

Thus, obstetrical complications may develop in lupus women in whom pregnancy is maintained, and their prognosis has been reported to be poor. However, few studies have examined the neonatal prognosis in lupus women who delivered at full term.

In 2005, Coleman et al.[12] reported that, at birth, a statistical difference was not observed in the weight and height of 23 neonates born to lupus women and 115 neonates born to healthy mothers. The explanation provided for this result was that the number of subjects in the lupus group was small, and factors influencing the prognosis of pregnant women such as nutrition, parity, and maternal comorbidity were not assessed. However, in our study, a comparison of the lupus group, in which pregnancy was maintained to full term by administering prenatal care for diverse obstetrical complications with the control group showed that birth weight and gestational age of the lupus group were lower and incidence of SGA was higher.

The perinatal prognosis of lupus mothers is poor in comparison with normal pregnant women. Therefore, even if the pregnancy could be maintained until full term by avoiding obstetrical complications that might develop during pregnancy and delivery, cautious evaluation and treatment of the neonates are essential.

## REFERENCES


1. Molad Y, Borkowski T, Monselise A, Ben-Haroush A, Sulkes J, Hod M, et al. Maternal and fetal outcome of lupus pregnancy: a prospective study of 29 pregnancies. Lupus 2005;14:145-51.
2. Khamashta MA. Systemic lupus erythematosus and pregnancy. Best Pract Res Clin Rheumatol 2006;20:685-94.
3. Petri M. Systemic lupus erythematosus and pregnancy. Rheum Dis Clin North Am 1994;20:87-118.
4. Mok CC, Wong RW. Pregnancy in systemic lupus erythematosus. Postgrad Med J 2001;77:157-65.
5. Petri M, Allbritton J. Fetal outcome of lupus pregnancy: a retrospective case-control study of the Hopkins Lupus Cohort. J Rheumatol 1993;20:650-6.
6. Georgiou PE, Politi EN, Katsimbri P, Sakka V, Drosos AA. Outcome of lupus pregnancy: a controlled study. Rheumatology (Oxford) 2000;39:1014-9.
7. Kim WU, Min JK, Kwun NK, Park SH, Hong YS, Lee SH, et al. Obstetric outcomes in patients with systemic lupus erythematosus. J Korean Rheum Assoc 1997;4:131-8.
8. Clowse ME, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum 2005;52:514-21.
9. Cortés-Hernández J, Ordi-Ros J, Paredes F, Casellas M, Castillo F, Vilardell-Tarres M. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology (Oxford) 2002;41:643-50.
10. Cervera R, Font J, Carmona F, Balasch J. Pregnancy outcome in systemic lupus erythematosus: good news for the new millennium. Autoimmun Rev 2002;1:354-9.
11. Moroni G, Ponticelli C. The risk of pregnancy in patients with lupus nephritis. J Nephrol 2003;16:161-7.
12. Coleman LA, Naleway AL, Davis ME, Greenlee RT, Wilson D, McCarty DJ. Birth weight and systemic lupus erythematosus. Lupus 2005;14:526-8.
13. Brucato A, Doria A, Frassi M, Castellino G, Franceschini F, Faden D, et al. Pregnancy outcome in 100 women with autoimmune diseases and anti-Ro/SSA antibodies: a prospective controlled study. Lupus 2002;11:716-21.
14. Mintz G, Niz J, Gutierrez G, Garcia-Alonso A, Karchmer S. Prospective study of pregnancy in systemic lupus erythematosus. Results of a multidisciplinary approach. J Rheumatol 1986;13:732-9.
15. Kim CR, Chang YP, Kim HS, Kim MJ, Kim BI, Choi JH, et al. Outcome in infants of mothers with systemic lupus erythematosus. J Korean Pediatr Soc 1993;36:791-804.