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# Predicting factors of adverse pregnancy outcomes in Thai patients with systemic lupus erythematosus

## A STROBE-compliant study

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**Abstract**

Studies on predicting factors for adverse pregnancy outcomes (APOs) in Thai patients with systemic lupus erythematosus (SLE) are limited. This retrospective observation study determined APOs and their predictors in Thai patients with SLE.

Medical records of pregnant SLE patients in a lupus cohort, seen from January 1993 to June 2017, were reviewed.

Ninety pregnancies (1 twin pregnancy) from 77 patients were identified. The mean age at conception was 26.94 ± 4.80 years. At conception, 33 patients (36.67%) had active disease, 23 (25.56%) hypertension, 20 (22.22%) renal involvement, and 6 of 43 (13.95%) positive anti-cardiolipin antibodies or lupus anti-coagulants, and 37 (41.11%) received hydroxychloroquine. Nineteen patients (21.11%) had pregnancy loss. Of 71 successful pregnancies, 28 (31.11%) infants were full-term, 42 (46.67%) pre-term and 1 (11.11%) post-term; 19 (26.39%) were small for gestational age (SGA), and 38 (52.58%) had low birth weight (LBW). Maternal complications occurred in 21 (23.33%) pregnancies [10 (11.11%) premature rupture of membrane (PROM), 8 (8.89%) pregnancy induced hypertension (PIH), 4 (4.44%) oligohydramnios, 2 (2.22%) post-partum hemorrhage, and 1 (1.11%) eclampsia]. Patients aged ≥ 25 years at pregnancy and those ever having renal involvement had predicted pregnancy loss with adjusted odds ratio (AOR) [95% CI] of 4.15 [1.10–15.72], $P = .036$ and 9.21 [1.03–82.51], $P = .047$, respectively. Renal involvement predicted prematurity (6.02 [1.77–20.52, $P = .004$), SGA (4.46 [1.44–13.78], $P = .009$), and LBW in infants (10.01 [3.07–32.62], $P < .001$). Prednisolone (>10 mg/day) and immunosuppressive drugs used at conception protected against prematurity (0.11 [0.02–0.85], $P = .034$). Flares and hematologic involvement predicted PROM (8.45 [1.58–45.30], $P = .013$) and PIH (9.24 [1.70–50.24], $P = .010$), respectively. Cutaneous vasculitis (33.87 [1.05–1,094.65], $P = .047$), and renal (31.89 [6.66–152.69], $P < .001$), mucocutaneous (9.17 [1.83–45.90], $P = .007$) and hematologic involvement (128.00 [4.60–3,564.46], $P = .004$) during pregnancy predicted flare; while prednisolone (>10 mg/day) and immunosuppressive drug use at conception reduced that risk (0.08 [0.01–0.68, $P = .021$).

APOs remain a problem in Thai pregnant SLE patients. Renal involvement and SLE flares were associated with the risk of APOs.

**Abbreviations:** 95% CI = 95% confidence intervals, ACL = anti-cardiolipin antibodies, ACR = American College of Rheumatology, ANA = antinuclear antibodies, Anti-dsDNA = anti-double stranded DNA antibodies, Anti-Ro = anti-Ro antibodies, Anti-Sm = anti-Smith antibodies, AOR = adjusted odds ratio, APL = anti-phospholipid antibodies, APO = adverse pregnancy outcomes, APS = anti-phospholipid syndrome, HCQ = hydroxychloroquine, HELLP syndrome = hemolysis, elevated liver enzymes, and low platelet count syndrome, IM drugs = immunosuppressive drugs, LAC = lupus coagulants, LBW = low birth weight, mSLEDAI-2K = modified Systemic Lupus Erythematosus Disease Activity Index-2000, OR = odds ratio, PGA = physician global assessment, PIH = pregnancy induced hypertension, PPH = post-partum hemorrhage, PROM = premature rupture of membrane, SDI = the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, SFI = the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLE flare index, SGA = small for gestational age, SLE = systemic lupus erythematosus, VLBW = very low birth weight.

**Keywords:** high-risk pregnancy, lupus nephritis, pregnancy outcome, systemic lupus erythematosus

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

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## 1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organ systems, characterized by remission and relapse. The disease predominantly affects women of child bearing age. Pregnancy in SLE patients is a challenging issue in clinical practice because of its association with increasing adverse outcomes in both mother and fetus.[1,2] Pregnant women with SLE have a reportedly higher rate of spontaneous abortion, fetal loss, intra-uterine growth retardation, pre-term delivery, pregnancy induced hypertension (PIH), pre-eclampsia and flares. Furthermore, pregnancy in SLE patients can cause disease exacerbation or flare, which often requires increasing doses of corticosteroids and/or immunosuppressive drugs that can have adverse effects on mother and fetus.[3,4] Thus, it is suggested that pregnancy in SLE patients should be avoided if the patients have had active severe disease within the previous 6 months, or significant heart, lung, renal and central nervous system involvement.[3,4]

With progress made in understanding the clinical course of SLE, standard instruments that determine disease activity and flares have been developed, as well as progression in medical treatment that results in improved obstetrics care of pregnant SLE patients.[3,5] Pregnancy outcomes in SLE patients have been reported widely, however, data on pregnancy outcomes from Asian countries are very limited.[6–11]

The purpose of this study was to determine pregnancy outcomes and identify independent predicting factors for adverse pregnancy outcomes (APOs) from a lupus cohort of Thai pregnant patients with SLE.

## 2. Patients and methods

### 2.1. Patients and data source

The medical records of SLE patients in a lupus cohort seen between January 1993 and June 2017 at the Division of Rheumatology, Faculty of Medicine, Chiang Mai University, Thailand were reviewed. SLE was diagnosed according to the 1997 updating the American College of Rheumatology (ACR) revised criteria for the classification of SLE.[12] Pregnant SLE patients were identified. Clinical manifestations, laboratory investigations, treatment, and SLE disease activity were recorded from 6 months prior to conception (−6 M) until 6 weeks after termination of pregnancy or delivery or the post-partum period. Pregnancy data were recorded at the time of conception or when the pregnancy was documented. The data were captured at −6 M, 3 months prior to conception (−3 M), at the time of conception, 1st trimester, 2nd trimester, 3rd trimester, and the post-partum period. If the patients had more than 1 visit during each period, the mean SLE disease activity of each period was used for statistical analysis. Laboratory investigations, including complete blood counts, urine analysis, and renal and liver functions were recorded routinely. The 24-hour urine protein creatinine ratio (24hour UPCI) [urine protein in gm/day to urine creatinine in gm/day] was determined only in cases with lupus nephritis (urine protein >0.5 gm/day). SLE patients were followed up usually in the clinic at 1 to 3 month intervals, depending on SLE disease activity or other clinical encounters. If the patients had more than 1 pregnancy, each one was considered as a separate observation and counted as an individual case.

Patients in the clinic should have been in clinical remission or have stable low disease activity (prednisolone ≤10 mg/day without immunosuppressive drugs other than anti-malarial medication) for a minimum of 12 months to allow for pregnancy to occur. Those who developed mild to moderate flares during pregnancy were administered prednisolone at a dosage of up to 0.50 mg/kg/day, and those with severe flares received >0.50 to 1.00 mg/kg/day. Anti-malarial medication was given according to clinical indications, e.g., skin rashes, oral ulcers or alopecia. Immunosuppressive drugs, particularly azathioprine and cyclosporine, were given to cases of severe flares. Cases in which the patients received methotrexate, cyclophosphamide or mycophenolate mofetil at the time of pregnancy, had these immunosuppressive drugs discontinued immediately and replaced with azathioprine or cyclosporine.

### 2.2. SLE disease activity and flare assessment

The modified Systemic Lupus Erythematosus Disease Activity Index-2000 (mSLEDAI-2K)[13] was used in this study to determine SLE disease activity (as anti-dsDNA and complements were not routinely available at this institution). The severity of SLE disease activity was classified according to that of Abrahamowicz et al,[14] but the mSLEDAI-2K instrument was used instead of the original SLEDAI-2K; remission [mSLEDAI-2K = 0], mild disease activity [mSLEDAI-2K = 1–5], moderate disease activity [mSLEDAI-2K = 6–10], high disease activity [mSLEDAI-2K = 11–19] and very high disease activity [mSLEDAI-2K = ≥20]). The severity of SLE flare (mild or moderate flare and severe flare) followed the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLE flare index (SFI).[15] As the physician global assessment (PGA) was not recorded routinely, the SFI was modified by excluding the PGA items (mSFI). Organ damage accrual was determined using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI).[16]

### 2.3. Pregnancy outcomes

The definition of maternal complications (premature rupture of membrane [PROM], oligohydramnios, pregnancy induced hypertension [PIH], pre-eclampsia, eclampsia, and direct and indirect maternal death), and fetal outcomes (pregnancy loss, miscarriage or spontaneous abortion, intra-uterine fetal death, medical termination of pregnancy, pre-term delivery, term delivery, post-term delivery, neonatal death, small for gestational age [SGA], and infant birth weight) followed that of standard references.[17]

### 2.4. Ethical statement

This study was performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Ethic Committee of the Faculty of Medicine, Chiang Mai University (no. 215/2017).

### 2.5. Statistical analysis

STATA 14.2 computer software (Stata Corporation, Texas USA) was used for data processing and statistical analysis. As some patients had more than 1 pregnancy, each one was considered individually for statistical analysis. Continuous variables were

presented as mean ± standard deviation (SD) or median (min-max), with categorical variables presented as percent. The Student *t* test and Wilcoxon rank sum test were used to determine the differences between 2 independent samples of continuous variables. One-way analysis of variance (ANOVA) and the Kruskal–Wallis test were used for more than 2 samples, with normal and non-normal distribution, respectively. The Chi-Squared test or Fisher exact test was used to determine associations among the categorical variables, where appropriate. Firth's logistic regression was used to predict the odds ratio (OR) and 95% confidence intervals (95% CI) when the outcome contained cell counts of zero. Variables with a $P$ value $<.20$ from univariate analysis were entered into multiple logistic regression analysis, and reported as adjusted odds ratio (AOR) and 95% CI. A $P \leq .05$ was considered as being a statistically significant difference.

## 3. Results

### 3.1. Demographics and characteristics of pregnant SLE patients

From a cohort of 1167 female SLE patients, 90 pregnancies occurred from 77 patients (1, 2, and 3 pregnancies in 66, 9 and 2 patients, respectively). Their mean age at SLE onset and age at pregnancy was 21.63 ± 5.89 years and 26.94 ± 4.80 years, respectively. Pregnancies occurred at the time of SLE diagnosis, and < 5 years and ≥ 5 years after SLE diagnosis in 7 (7.78%), 49 (54.44%) and 34 (37.78%) pregnancies, respectively. Of the 90 pregnancies, 45 (50.00%), 25 (27.78%), and 20 (22.22%) were the first, second and third or more, respectively. Their mean cumulative ACR classification criteria and SDI score were 5.49 ± 1.15 and 0.40 ± 0.72, respectively. The mean ± SD mSLEDAI-2K score at −6 M and time of conception was 1.72 ± 3.22 and 1.90 ± 3.44, respectively. Active disease at the time of conception (mSLEDAI-2K score ≥ 0) was observed in 33 of 90 pregnancies (36.67%), and all of them were unplanned. Active organ involvement at the time of conception was renal (urine protein creatinine ratio >0.5) in 20 (22.22%) pregnancies, mucocutaneous lesions in 15 (16.67%), cutaneous vasculitis in 2 (2.22%), and arthritis and hematologic abnormalities in 1 (1.11%) of each.

Co-morbidities were seen as follows: hypertension in 23 (25.56%) pregnancies, dyslipidemia in 8 (8.89%), thalassemia in 7 (7.78%), anti-phospholipid syndrome in 3 (3.33%), diabetes mellitus in 1 (1.11%), and others in 19 (21.11%) [hepatitis C virus infection, avascular necrosis of the hip, stroke and atrial secundum defect, and past history of cryptococcal meningitis, pneumocystis jirovecii pneumonia, and past treatment of pulmonary tuberculosis]. None of the patients drank alcohol or smoked.

Antinuclear antibodies (ANA) were observed in 89 pregnancies (98.89%). Anti-double stranded DNA (anti-dsDNA), anti-Smith (anti-Sm), anti-cardiolipin (ACL), lupus coagulants (LAC), and anti-Ro (anti-Ro) antibodies were observed in 50 of 85 (58.82%), 1 of 12 (8.33%), 4 of 58 (6.89%), 3 of 42 (7.14%), and 21 of 46 (45.65%) pregnancies that had been tested, respectively.

Patients in 15 of the 90 pregnancies (16.67%) had not received any specific SLE medication at the time of conception. Patients in 57 (63.33%) of the pregnancies received prednisolone at a dose of ≤10 mg/day, and in 16 (17.78%) at ≥ 10 mg/day, with the mean dosage of 10.77 ± 11.73 mg/day. Patients also received hydroxychloroquine (HCQ) in 37 (41.11%) pregnancies, cyclophosphamide in 6 (6.67%), mycophenolate mofetil in 4 (4.40%), azathioprine in 10 (11.11%), and cyclosporine in 3 (3.33%). Both cyclophosphamide and mycophenolate mofetil were switched to azathioprine or cyclosporine when the pregnancy was documented.

### 3.2. Overall pregnancy outcomes

Of the 90 pregnancies, 19 (21.11%) were lost (spontaneous abortion in 12 (13.33%) [7 in the 1st trimester and 5 in the 2nd], medical termination in 5 (5.56%) [1 in the 1st trimester and 4 in the 2nd], and dead fetus in the utero (1 in each 2nd and 3rd trimester). Of the 71 (78.89%) successful pregnancies, 28 (31.11%) were full-term, 42 (46.67%) pre-term (1 twin pregnancy), and 1 (1.11%) was a post-term delivery, resulting in 72 live born infants. Mode of delivery among the live births were vaginal in 52 (73.24%) and cesarean section in 19 (26.76%). The mean ± SD duration of pregnancy with live born infants was 35.76 ± 3.58 weeks. The mean ± SD weight of the 72 live born infants was 2,367.33 ± 640.30 gm (range 720–3853 gm), with normal birth weight (≥2500 gm), low birth weight (LBW) [1500–2499 gm], and very low birth weight (VLBW) [<1500 gm] in 34 (47.22%), 30 (41.67%) and 8 (11.11%) infants, respectively. SGA infants occurred in 19 live born infants (26.39%). There was 1 neonatal death (1.11%). No infants had congenital anomalies or completed heart block.

Maternal complications occurred in 21 (23.33%) pregnancies. PROM occurred in 10 (11.11%) pregnancies, PIH in 8 (8.89%), oligohydramnios in 4 (4.44%), post-partum hemorrhage in 2 (2.22%), and eclampsia in 1 (1.11%). One concomitant PROM and oligohydramnios, PROM and post-partum hemorrhage, PROM and PIH, and PIH and eclampsia occurred in each pregnancy. There were no cases of anti-partum hemorrhage, post-partum endometritis, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), pre-eclampsia or maternal death. Thirty seven flares (41.11%) were mild to moderate and severe in 9 (24.32%) and 28 (75.68%) pregnancies, respectively.

### 3.3. Effect of renal involvement, hypertension, presence of anti-cardiolipin antibodies and/or lupus anti-coagulants and SLE flares on pregnancy outcomes

The effects of renal involvement, hypertension, and the presence of ACL/LAC and SLE flares on pregnancy outcomes were determined and are shown in Table 1.

Forty pregnancies were shown to have active nephritis during pregnancy. Active renal involvement occurred in 30, 30, and 26 pregnancies during the 1st, 2nd, and 3rd trimester, respectively, which was significantly higher than the 20 pregnancies seen at the time of conception ($P < .001$). When compared to patients without renal involvement during pregnancy, those with it had significantly shorter mean pregnancy duration (34.34 ± 4.40 weeks vs 36.80 ± 2.26 weeks, $P = .003$), lower fetal birth weight among live births (2029.52 ± 611.82 gm vs 2622.76 ± 540.06 gm, $P < .001$), and a higher proportion of LBW infants (60.98% vs 26.00%, $P < .001$), and SGA infants (32.50% vs 12.00%, $P = .018$). Although the proportion among live birth infants was not different, those with renal involvement had a significantly lower proportion of full-term infants (15.00% vs 44.00%, $P = .003$) and almost significantly higher proportion of pre-term

**Table 1**

**Effect of active renal involvement during pregnancy, hypertension at the time of conception, presence of anti-phospholipid antibodies and SLE flares during pregnancy on pregnancy outcomes.**

| | Renal involvement | | | Hypertension | | | ACL/LAC | | | Flares | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Yes | No | *P* value | Yes | No | *P* value | Yes | No | *P* value | Yes | No | *P* value |
| Successful pregnancy, n (%) | 30 (75.00) | 41 (82.00) | .419 | 16 (69.57) | 55 (82.09) | .204 | 4 (66.67) | 32 (86.49) | .248 | 32 (86.49) | 39 (73.58) | .140 |
| Pregnancy duration, in weeks, mean ± SD | 34.34 ± 4.50 | 36.80 ± 2.26 | .009 | 35.60 ± 2.47 | 35.81 ± 3.86 | .838 | 38.50 ± 2.52 | 36.20 ± 3.45 | .209 | 34.43 ± 3.91 | 36.85 ± 2.90 | .004 |
| Fetal weight, in grams, mean ± SD | 2,029.52 ± 611.82 | 2,622.76 ± 540.06 | <.001 | 2,147.65 ± 580.34 | 2,435.24 ± 647.59 | .106 | 2,680.00 ± 557.32 | 2,379.94 ± 749.66 | .447 | 2097.58 ± 615.13 | 2595.59 ± 575.07 | .001 |
| Fetal outcomes | | | | | | | | | | | | |
| Live birth, n (%) | 31 (75.61)* | 41 (82.00) | .456 | 17 (70.83)* | 55 (82.09) | .244 | 4 (66.67) | 32 (86.49) | .248 | 33 (86.84)* | 39 (73.58) | .125 |
| Term, n (%) | 6 (15.00) | 22 (44.00) | .003 | 7 (30.43) | 21 (31.34) | .935 | 3 (50.00) | 14 (37.84) | .666 | 9 (24.32) | 19 (35.85) | .245 |
| Pre-term, n (%) | 24 (58.54)* | 19 (38.00) | .051 | 10 (41.67)* | 33 (49.25) | .523 | 1 (16.67) | 17 (45.95) | .177 | 24 (63.16)* | 19 (35.85) | .010 |
| Post-term, n (%) | 1 (2.50) | 0 | .444 | 0 | 1 (1.49) | >.999 | 0 | 1 (2.70) | >.999 | 0 | 1 (1.89) | >.999 |
| Total fetal loss, n (%) | 10 (25.00) | 9 (18.00) | .419 | 7 (30.43) | 12 (17.91) | .204 | 2 (33.33) | 5 (13.51) | .248 | 5 (13.51) | 14 (26.42) | .140 |
| Spontaneous abortion, n (%) | 6 (15.00) | 6 (12.00) | .677 | 4 (17.39) | 8 (11.94) | .507 | 1 (16.67) | 4 (10.81) | .547 | 3 (8.11) | 9 (16.98) | .223 |
| Medical termination, n (%) | 2 (5.00) | 3 (6.00) | >.999 | 2 (8.70) | 3 (4.48) | .599 | 1 (16.67) | 1 (2.70) | .262 | 1 (2.70) | 4 (7.55) | .645 |
| Dead fetus in the utero, n (%) | 2 (5.00) | 0 | .195 | 1 (4.35) | 1 (1.49) | .448 | 0 | 0 | | 1 (2.70) | 1 (1.89) | >.999 |
| Neonatal death, n (%) | 1 (2.50) | 0 | .444 | 1 (4.35) | 0 | .256 | 0 | 1 (2.70) | >.999 | 1 (2.70) | 0 | .411 |
| SGA, n (%) | 13 (32.50) | 6 (12.00) | .018 | 7 (30.43) | 12 (17.91) | .204 | 1 (16.67) | 12 (32.43) | .649 | 11 (29.73) | 8 (15.09) | .094 |
| LBW (< 2500 grams), n (%) | 25 (60.98)* | 13 (26.00) | .001 | 11 (45.83)* | 27 (40.30) | .637 | 1 (16.67) | 18 (48.65) | .143 | 23 (60.53)* | 15 (28.30) | .002 |
| Maternal complications†, n (%) | 30 (75.00) | 15 (30.00) | <.001 | 16 (69.57) | 29 (43.28) | .030 | 2 (33.33) | 18 (48.65) | .669 | 37 (100.00) | 8 (15.09) | <.001 |
| PROM, n (%) | 6 (15.00) | 4 (8.00) | .294 | 1 (4.35) | 9 (13.43) | .232 | 0 | 4 (10.81) | >.999 | 8 (21.62) | 2 (3.77) | .008 |
| Oligohydramnios, n (%) | 3 (7.50) | 1 (2.00) | .319 | 1 (4.35) | 3 (4.48) | >.999 | 0 | 2 (5.41) | >.999 | 2 (5.41) | 2 (3.77) | >.999 |
| PPH, n (%) | 0 | 2 (4.00) | .501 | 0 | 2 (2.99) | >.999 | 0 | 1 (2.70) | >.999 | 0 | 2 (3.77) | .510 |
| PIH, n (%) | 5 (12.50) | 3 (6.00) | .282 | 1 (4.35) | 7 (10.45) | .375 | 0 | 3 (8.11) | >.999 | 5 (13.51) | 3 (5.66) | .198 |
| Eclampsia, n (%) | 0 | 1 (2.00) | >.999 | 0 | 1 (1.49) | >.999 | 0 | 1 (2.70) | >.999 | 0 | 1 (1.89) | >.999 |
| Flares, n (%) | 27 (67.50) | 10 (20.00) | <.001 | 14 (60.87) | 23 (34.33) | .026 | 2 (33.33) | 14 (37.84) | >.999 | | | |

* twin pregnancy.

† maternal complications (PROM + oligohydramnios = 1, PROM + post-partum hemorrhage = 1, PROM + PIH = 1, PIH + eclampsia = 1), ACL/LAC = anti-cardiolipin antibodies/lupus anti-coagulants, LBW = low birth weight, PIH = pregnancy induced hypertension, PPH = post-partum hemorrhage, PROM = premature rupture of membrane, SGA = small for gestational age.

infants (58.54% vs 38.00%, $P=.051$). There was no statistically significant difference in fetal loss among the 2 groups. The maternal complications in those with renal involvement during pregnancy were significantly higher (75.00% vs 30.00%, $P<.001$), which was due to a higher proportion of patients with SLE flare (67.50% vs 20.00%, $P<.001$). Other maternal complications, including PROM, oligohydramnios and PIH, also were higher proportionally, but they did not reach statistical significance.

Overall, there were no statistically significant differences in adverse fetal outcomes among patients with or without hypertension during pregnancy. However, pregnancy outcomes among patients with hypertension tended to have a lower proportion of live birth infants, and higher proportion of fetal loss (both spontaneous and medical terminations), SGA and LBW among full-term infants, and a lower mean fetal birth weight. Maternal complications were significantly higher in patients with hypertension (69.57% vs 43.28%, $P=.030$), which was due mainly to the higher proportion of those with SLE flares (60.48% vs 34.33%, $P=.026$). It was interesting that the proportion of PROM and PIH was lower in patients with hypertension, but with no significance.

The effect of anti-cardiolipin antibodies (ACL) and lupus anticoagulant (LAC) tests on pregnancy outcomes also was determined. Unfortunately, these 2 tests were determined in only approximately 50% of the patients. ACA and LAC were positive in a small proportion of the patients (4 of 58 or 6.89% and 3 of 42 or 7.14% of those tested, respectively). Overall, there was no statistically significant difference between either the fetal and maternal outcomes among pregnant patients with positive ACL/LAC or those without; however, those with positive ACL/LAC tended to have a lower proportion of live births and full-term birth infants, and higher proportion of fetal losses. It was interesting that the proportion of SGA, LBW, and maternal complication in the ACL/LAC positive patients also was lower, but without statistical significance. This might be due to the small number of patients in this group.

The effect of flares on pregnancy outcomes also was determined. When compared to SLE patients without flares during pregnancy, those with them had significantly shorter duration of pregnancy ($34.43\pm3.91$ weeks vs $36.85\pm2.90$ weeks, $P=.004$), and lower mean fetal weight among live births ($2097.58\pm615.13$ gm vs $2595.59\pm575.07$ gm, $P=.001$). Although the proportion of live birth infants and fetal loss was no different between the 2 groups, the patients with flares had a significantly higher proportion of pre-term births and LBW infants (63.16% vs 35.85%, $P=.010$, and 60.53% vs 28.30%, $P=.002$, respectively). The proportion of SGA infants also was higher, but did not reach statistical significance (29.73% vs 15.09%, $P=.094$). The adverse maternal outcomes were higher (100.00% vs 15.09%, $P<.001$), particularly of PROM (21.62% vs 3.77%, $P<.008$).

### 3.4. Effect of HCQ used on pregnancy outcomes

The effect of HCQ used during pregnancy on pregnancy outcomes was determined. Overall, there was no statistically significant difference in fetal outcomes among patients who did or did not receive HCQ during pregnancy. However, infants born to mothers who used HCQ tended to have a higher proportion of full term births (37.84% vs 26.42%, $P=.249$), and lower proportion of SGA (16.22% vs. 24.53%, $P=.342$) and LBW (36.84% vs 45.28%, $P=.421$). The proportion of live birth infants and fetal loss was similar between the 2 groups (78.95% vs 79.25%, $P=.972$, and 21.62% vs. 20.75%, $P=.921$, respectively). The proportion of maternal complications was lower among patients who received HCQ, and it almost reached statistical significance (37.84% vs 58.49%, $P=.054$). The proportion of maternal PROM, PIH and flares in the HCQ group also was lower, but did not reach statistical significance (5.41% vs 15.09%, $P=.150$; 5.41% vs 11.32%, $P=.332$, and 32.43% vs 47.17%, $P=.162$, respectively).

### 3.5. Pregnancy outcomes according to period of pregnancy, and between the first and subsequence pregnancy

The pregnancy outcomes according to the period of pregnancy (1993–2001, 2002–2009, and 2010–2017) were determined. Overall, there was no statistically significant difference in fetal or maternal outcomes between each pregnancy period. However, when comparing the pregnancy outcomes between 2010–2017, 2002–2009, and 1993–2001, fetal outcomes among pregnancies during 2010–2017 tended to have a higher proportion of live births (80.85% vs 76.00% vs 78.95%, $P=.890$), full-term birth infants (36.17% vs 32.00% vs 16.67%, $P=.313$), but with a lower proportion of pre-term birth infants (42.55% vs 44.00% vs 63.16%, $P=.294$), and pregnancy loss (19.15% vs 24.00% vs 22.22%, $P=.884$). They also had had a higher proportion of SGA and LBW (29.79% vs 16.00% vs 5.56%, $P=.070$, and 48.94% vs 36.00% vs 31.58%, $P=.342$, respectively). The proportion of maternal complications was similar (48.94% vs 48.00% vs 55.56%, $P=.868$); but with a tendency for decreased proportion of PROM (8.51% vs 12.00% vs 16.67%, $P=.495$), PIH (8.51% vs 4.00% vs 16.67%, $P=.382$) and SLE flares (38.30% vs 44.00% vs 44.44%, $P=.851$).

The pregnancy outcomes between patients with a first pregnancy and subsequent pregnancies also were compared. Similarly, there was no significant difference in fetal and maternal outcomes between the 2 groups. However, fetal outcomes in subsequent pregnancy groups tended to have a lower proportion of live births (73.91% vs 84.44%, $P=.217$), full-term births (24.44% vs 37.78%, $P=.172$), SGA (17.78% vs 24.44%, $P=.438$) and LBW infants (36.96% vs 46.67%, $P=.348$), but higher proportion of fetal loss (26.67% vs 15.56%, $P=.197$). Maternal complications tended to be lower (46.67% vs 53.33%, $P=.527$), which was due mainly to decreased proportion of SLE flares (37.78% vs 44.44%, $P=.520$). The rate of caesarean section was significantly higher among subsequent pregnancies (39.39% vs 15.79%, $P=.025$).

### 3.6. Predicting factors for adverse pregnancy outcomes

In order to determine independent predicting factors for APOs, the clinical characteristics that associated with adverse fetal outcomes (pregnancy loss, prematurity, SGA and LBW), and adverse maternal outcomes (PROM, PIH and flare) were compared and are shown in Tables 2 and 3, respectively.

Factors that might be associated with adverse fetal and maternal outcomes, and those that had a statistical difference with a $P$ value of $<.2$ in the univariate analysis (Tables 2 and 3) were included in the multiple logistic regression analysis (Tables 4 and 5). Independent predicting factors that increased the risk of fetal loss included age at pregnancy of $\geq 25$ years (AOR [95% CI])

**Table 2**

**Comparison of clinical characteristics of adverse fetal outcomes in pregnant SLE patients.**

| Characteristics | Successful pregnancy (n = 71) | Pregnancy loss (n = 19) | *P* value | Pre-maturity (n = 42) | Full term + post term (n = 29) | *P* value | SGA (n = 19) | Non-SGA (n = 52) | *P* value | LBW (n = 37) | Normal BW (n = 34) | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age at pregnancy (in years), mean ± SD | 26.30 ± 4.55 | 29.31 ± 5.09 | .014 | 26.46 ± 4.73 | 26.07 ± 4.34 | .726 | 25.09 ± 3.85 | 26.74 ± 4.73 | .178 | 26.12 ± 4.61 | 26.50 ± 4.54 | .726 |
| Disease duration prior to conception (in years), mean ± SD | 4.92 ± 5.01 | 6.99 ± 5.37 | .081 | 4.38 ± 3.96 | 5.71 ± 6.21 | .574 | 5.20 ± 4.26 | 4.82 ± 5.29 | .451 | 4.54 ± 4.08 | 5.34 ± 5.89 | .954 |
| Co-morbidities | | | | | | | | | | | | |
| Hypertension, n (%) | 16 (22.54) | 7 (36.84) | .204 | 9 (21.43) | 7 (24.14) | .788 | 7 (36.84) | 9 (17.31) | .081 | 10 (27.03) | 6 (17.65) | .345 |
| Diabetes, n (%) | 1 (1.41) | 0 | >.999 | 1 (2.38) | 0 | >.999 | 1 (5.26) | 0 | .268 | 1 (2.70) | 0 | >.999 |
| Dyslipidemia, n (%) | 5 (7.04) | 3 (15.79) | .234 | 3 (7.14) | 2 (6.90) | >.999 | 4 (21.05) | 1 (1.92) | **.016** | 4 (10.81) | 1 (2.94) | .359 |
| APS, n (%) | 2 (2.82) | 1 (5.26) | .513 | 0 | 2 (6.90) | .163 | 0 | 2 (3.85) | >.999 | 0 | 2 (5.88) | .226 |
| ANA positive, n (%) | 70 (98.59) | 19 (100.00) | >.999 | 41 (97.62) | 29 (100.00) | >.999 | 19 (100.00) | 51 (98.08) | >.999 | 37 (100.00) | 33 (97.06) | .479 |
| Anti-dsDNA, n (%)* | 41/67 (61.19) | 9/18 (50.00) | .392 | 26/40 (65.00) | 15/27 (55.56) | .436 | 13/19 (68.42) | 28/48 (58.33) | .445 | 25/37 (67.57) | 16/30 (53.33) | .234 |
| Anti-Sm, n (%)* | 0/11 | 1/1 (100.00) | .083 | 0/7 | 0/4 | | 0/2 | 0/9 | | 0/6 | 0/5 | |
| ACL/LAC, n (%)* | 4/36 (11.11) | 2/7 (28.57) | .248 | 1/18 (5.56) | 3/18 (16.67) | .603 | 1/13 (7.69) | 3/23 (13.04) | >.999 | 1/19 (5.26) | 3/17 (17.65) | .326 |
| Anti-Ro, n (%)* | 16/38 (42.11) | 5/8 (62.50) | .293 | 7/17 (41.18) | 9/21 (42.86) | .917 | 6/13 (46.15) | 10/25 (40.00) | .715 | 11/23 (47.83) | 5/15 (33.33) | .376 |
| Anti-La, n (%)* | 16/38 (42.11) | 4/9 (44.44) | .898 | 7/17 (41.18) | 9/21 (42.86) | .917 | 6/13 (46.15) | 10/25 (40.00) | .715 | 11/23 (47.83) | 5/15 (33.33) | .376 |
| Pregnancy loss (ever), n (%) | 23 (32.39) | 9 (47.37) | .226 | 12 (28.57) | 11 (37.93) | .407 | 6 (31.58) | 17 (32.69) | .929 | 11 (29.73) | 12 (35.29) | .617 |
| Cumulative number of ACR criteria, mean ± SD | 5.46 ± 1.11 | 5.58 ± 1.35 | .704 | 5.38 ± 1.17 | 5.59 ± 1.02 | .446 | 5.42 ± 1.02 | 5.48 ± 1.15 | .842 | 5.35 ± 1.06 | 5.59 ± 1.16 | .371 |
| Disease activity (mSLEDAI-2K) at −6M, mean ± SD | 1.34 ± 2.43 | 3.16 ± 5.05 | .325 | 1.36 ± 2.44 | 1.31 ± 2.46 | .960 | 1.42 ± 2.48 | 1.31 ± 2.44 | .874 | 1.38 ± 2.53 | 1.29 ± 2.36 | .933 |
| Disease activity (mSLEDAI-2K) at conception, mean ± SD | 1.58 ± 2.74 | 3.16 ± 5.22 | .562 | 1.81 ± 2.98 | 1.24 ± 2.36 | .385 | 2.16 ± 2.99 | 1.36 ± 2.64 | .222 | 1.92 ± 3.22 | 1.20 ± 2.08 | .566 |
| Remission, n (%) | 45 (63.38) | 12 (63.16) | .321 | 25 (59.52) | 20 (68.97) | .629 | 10 (52.63) | 35 (67.31) | .444 | 23 (62.16) | 22 (64.71) | .955 |
| Mild, n (%) | 19 (26.76) | 3 (15.79) | | 13 (30.95) | 6 (20.69) | | 6 (31.58) | 13 (25.00) | | 10 (27.03) | 9 (26.47) | |
| Moderate and high, n (%) | 7 (9.86) | 4 (21.05) | | 4 (9.52) | 3 (10.34) | | 3 (15.79) | 4 (7.69) | | 4 (10.81) | 3 (8.82) | |
| SDI score at conception, mean ± SD | 0.35 ± 0.66 | 0.58 ± 0.90 | .400 | 0.36 ± 0.62 | 0.34 ± 0.72 | .612 | 0.21 ± 0.42 | 0.40 ± 0.72 | .463 | 0.24 ± 0.55 | 0.47 ± 0.75 | .169 |
| Active organ involvement during pregnancy | | | | | | | | | | | | |
| Renal | 30 (42.25) | 10 (52.63) | .419 | 23 (54.76) | 7 (24.14) | .010 | 13 (68.42) | 17 (32.69) | .007 | 24 (64.86) | 6 (17.65) | <.001 |
| Mucocutaneous | 23 (32.39) | 4 (21.05) | .338 | 12 (28.57) | 11 (37.93) | .407 | 4 (21.05) | 19 (36.54) | .217 | 9 (24.32) | 14 (41.18) | .130 |
| Vasculitis | 2 (2.82) | 1 (5.26) | .513 | 1 (2.38) | 1 (3.45) | >.999 | 1 (5.26) | 1 (1.92) | .466 | 1 (2.70) | 1 (2.94) | >.999 |
| Arthritis | 2 (2.82) | 0 | >.999 | 2 (4.76) | 0 | .510 | 0 | 2 (3.85) | >.999 | 1 (2.70) | 1 (2.94) | >.999 |
| Hematologic | 8 (11.27) | 0 | .125 | 6 (14.29) | 2 (6.90) | .333 | 4 (21.05) | 4 (7.69) | .197 | 5 (13.51) | 3 (8.82) | .532 |
| Medication at conception | | | | | | | | | | | | |
| Prednisolone, n (%) | 56 (78.87) | 17 (89.47) | .294 | 32 (76.19) | 24 (82.76) | .505 | 15 (78.95) | 41 (78.85) | .993 | 31 (83.78) | 25 (73.53) | .290 |
| Dose (in mg/day), mean ± SD | 9.11 ± 9.38 | 16.25 ± 16.58 | .058 | 9.53 ± 9.56 | 8.54 ± 9.32 | .412 | 12.50 ± 12.32 | 7.86 ± 7.88 | .162 | 9.11 ± 9.39 | 9.10 ± 9.57 | .823 |
| Prednisolone >10 mg/day | 10 (14.08) | 6 (31.58) | .076 | 6 (14.29) | 4 (13.79) | .953 | 5 (26.32) | 5 (9.62) | .073 | 6 (16.22) | 4 (11.76) | .590 |
| Hydroxychloroquine, n (%) | 29 (40.85) | 8 (42.11) | .921 | 15 (35.71) | 14 (48.28) | .290 | 6 (31.58) | 23 (44.23) | .337 | 13 (35.14) | 16 (47.06) | .307 |
| Dose (in mg/day), mean ± SD | 191.38 ± 86.67 | 256.25 ± 129.39 | .144 | 183.33 ± 79.43 | 200.00 ± 96.08 | .762 | 166.67 ± 51.64 | 197.83 ± 93.52 | .533 | 165.38 ± 55.47 | 212.50 ± 102.47 | .275 |
| Immunosuppressive drug† | 18 (25.35) | 4 (21.05) | .699 | 10 (23.81) | 8 (27.59) | .719 | 5 (26.32) | 13 (25.00) | .910 | 12 (32.43) | 6 (17.65) | .153 |
| Mycophenolate mofetil, n (%) | 4 (5.63) | 0 | .575 | 2 (4.76) | 2 (6.90) | >.999 | 1 (5.26) | 3 (5.77) | >.999 | 3 (8.11) | 1 (2.94) | .615 |
| Cyclophosphamide, n (%) | 3 (4.23) | 3 (15.79) | .106 | 3 (7.14) | 0 | .265 | 1 (5.26) | 2 (3.85) | >.999 | 3 (8.11) | 0 | .241 |
| Azathioprine, n (%) | 10 (14.08) | 0 | .083 | 5 (11.90) | 5 (17.24) | .525 | 3 (15.79) | 7 (13.46) | .803 | 6 (16.22) | 4 (11.76) | .590 |
| Cyclosporine, n (%) | 2 (2.82) | 1 (5.26) | .513 | 0 | 2 (6.90) | .163 | 0 | 2 (3.85) | >.999 | 1 (2.70) | 1 (2.94) | >.999 |
| Flare during pregnancy | 32 (45.07) | 5 (26.32) | .140 | 23 (54.76) | 9 (31.03) | .048 | 11 (57.89) | 21 (40.38) | .189 | 22 (59.46) | 10 (29.41) | .011 |

* number of positive tests/number tested.

† excluding hydroxychloroquine, −6 M = 6 months prior to conception, ACR = American College of Rheumatology, ACL/LAC = anti-cardiolipin antibodies/lupus anti-coagulants, APS = anti-phospholipid syndrome, BW = birth weight, LBW = low birth weight, SDI = Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index, mSLEDAI-2K = modified systemic lupus erythematosus disease activity index – 2000, SGA = small for gestational age.

**Table 3**

**Comparison of clinical characteristics of adverse maternal outcomes in pregnant SLE patients.**

| Characteristics | Premature rupture of membrane | | | Pregnancy induced hypertension | | | Flares | | |
|---|---|---|---|---|---|---|---|---|---|
| | Yes (n=10) | No (n=80) | *P* value | Yes (n=8) | No (n=82) | *P* value | Yes (n=37) | No (n=53) | *P* value |
| Age at pregnancy (in years), mean±SD | 28.85±4.38 | 26.70±4.82 | .182 | 25.92±3.65 | 27.03±4.90 | .535 | 26.89±4.75 | 26.97±4.88 | .937 |
| Disease duration prior to conception (in years), mean±SD | 3.81±3.06 | 5.55±5.31 | .521 | 4.67±6.25 | 5.43±5.04 | .257 | 5.67±5.45 | 5.14±4.92 | .608 |
| Co-morbidities | | | | | | | | | |
| Hypertension, n (%) | 1 (10.00) | 22 (27.50) | .232 | 1 (12.50) | 22 (26.83) | .375 | 14 (37.84) | 9 (16.98) | .026 |
| Diabetes, n (%) | 0 | 1 (1.25) | >.999 | 0 | 1 (1.22) | >.999 | 0 | 1 (1.89) | >.999 |
| Dyslipidemia, n (%) | 0 | 8 (10.00) | .295 | 0 | 8 (9.76) | .355 | 3 (8.11) | 5 (9.43) | .828 |
| APS, n (%) | 0 | 3 (3.75) | >.999 | 0 | 3 (3.66) | >.999 | 2 (5.41) | 1 (1.89) | .566 |
| ANA positive, n (%) | 10 (100.00) | 79 (98.75) | >.999 | 7 (87.50) | 82 (100.00) | .089 | 37 (100.00) | 52 (98.11) | >.999 |
| Anti-dsDNA, n (%)* | 5/9 (55.56) | 45/76 (59.21) | .833 | 5/7 (71.43) | 45/78 (57.69) | .479 | 20/35 (57.14) | 30/50 (60.00) | .792 |
| Anti-Sm, n (%)* | 0/1 | 1/11 (9.09) | >.999 | 0/1 | 1/11 (9.09) | >.999 | 0/4 | 1/8 (12.50) | >.999 |
| ACL/LAC, n (%)* | 0/4 | 6/39 (15.38) | >.999 | 0/3 | 6/40 (15.00) | >.999 | 2/16 (12.50) | 4/27 (14.81) | >.999 |
| Anti-Ro, n (%)* | 1/4 (25.00) | 20/42 (47.62) | .614 | 2/4 (50.00) | 19/42 (45.24) | >.999 | 6/15 (40.00) | 15/31 (48.39) | .592 |
| Anti-La, n (%)* | 1/4 (25.00) | 19/43 (44.19) | .626 | 2/4 (50.00) | 18/43 (41.86) | >.999 | 6/15 (40.00) | 14/32 (43.75) | .808 |
| Pregnancy loss (ever), n (%) | 3 (30.00) | 29 (36.25) | .697 | 2 (25.00) | 30 (36.59) | .513 | 9 (24.32) | 23 (43.40) | .063 |
| Cumulative number of ACR criteria, mean±SD | 5.30±1.06 | 5.51±1.17 | 0.586 | 5.62±0.52 | 5.48±1.20 | .518 | 5.54±1.14 | 5.45±1.17 | .725 |
| Disease activity (mSLEDAI-2K) at -6M, mean±SD | 0.40±1.26 | 1.89±3.35 | .116 | 0.25±0.71 | 1.86±3.33 | .163 | 1.70±3.44 | 1.74±3.09 | .696 |
| Disease activity (mSLEDAI-2K) at conception, mean±SD | 0.70±1.34 | 2.06±3.59 | .400 | 1.00±2.14 | 2.00±3.54 | .454 | 2.16±3.92 | 1.74±3.09 | .624 |
| Remission, n (%) | 7 (70.00) | 50 (62.50) | 0.450 | 6 (75.00) | 51 (62.20) | .704 | 22 (59.46) | 35 (66.04) | 0.816 |
| Mild, n (%) | 3 (30.00) | 19 (23.75) | | 1 (12.50) | 21 (25.61) | | 10 (27.03) | 12 (22.64) | |
| Moderate and high, n (%) | 0 | 11 (13.75) | | 1 (12.50) | 10 (12.20) | | 5 (13.51) | 6 (11.32) | |
| SDI score at conception, mean±SD | 0.50±0.85 | 0.39±0.70 | .728 | 0±0 | 0.44±0.74 | .079 | 0.54±0.80 | 0.30±0.64 | .120 |
| Active organ involvement during pregnancy | | | | | | | | | |
| Renal | 6 (60.00) | 34 (42.50) | .294 | 5 (62.50) | 35 (42.68) | .282 | 27 (72.97) | 13 (24.53) | <.001 |
| Mucocutaneous | 4 (40.00) | 23 (28.75) | .464 | 4 (50.00) | 23 (28.05) | .234 | 17 (45.95) | 10 (18.87) | .006 |
| Vasculitis | 0 | 3 (3.75) | >.999 | 0 | 3 (3.66) | >.999 | 3 (8.11) | 0 | .066 |
| Arthritis | 0 | 2 (2.50) | >.999 | 0 | 2 (2.44) | >.999 | 1 (2.70) | 1 (1.89) | >.999 |
| Hematologic | 2 (20.00) | 6 (7.50) | .190 | 3 (37.50) | 5 (6.10) | .003 | 8 (21.62) | 0 | <.001 |
| Medication at conception | | | | | | | | | |
| Prednisolone, n (%) | 8 (80.00) | 65 (81.25) | .924 | 4 (50.00) | 69 (84.15) | **.039** | 29 (78.38) | 44 (83.02) | .580 |
| Dose (in mg/day), mean±SD | 5.94±2.65 | 11.36±12.78 | .423 | 19.38±27.26 | 10.27±10.41 | .755 | 8.88±7.89 | 12.02±13.63 | .958 |
| Prednisolone >10 mg/day | 0 | 16 (20.00) | .119 | 1 (12.50) | 15 (18.29) | .683 | 5 (13.51) | 11 (20.75) | .377 |
| Hydroxychloroquine, n (%) | 2 (20.00) | 35 (43.75) | .150 | 2 (25.00) | 35 (42.68) | .332 | 12 (32.43) | 25 (47.17) | .162 |
| Dose (in mg/day), mean±SD | 125.00±106.07 | 210.00±98.37 | .223 | 150.00±70.71 | 208.57±100.36 | .382 | 208.33±129.39 | 204.00±84.06 | .797 |
| Immunosuppressive drug† | 2 (20.00) | 20 (25.00) | .729 | 0 | 22 (26.83) | .092 | 7 (18.92) | 15 (28.30) | .308 |
| Mycophenolate mofetil, n (%) | 1 (10.00) | 3 (3.75) | .381 | 0 | 4 (4.88) | >.999 | 2 (5.41) | 2 (3.77) | >.999 |
| Cyclophosphamide, n (%) | 0 | 6 (7.50) | .370 | 0 | 6 (7.32) | .428 | 1 (2.70) | 5 (9.43) | .208 |
| Azathioprine, n (%) | 1 (10.00) | 9 (11.25) | .906 | 0 | 10 (12.20) | .295 | 4 (10.81) | 6 (11.32) | .940 |
| Cyclosporine, n (%) | 0 | 3 (3.75) | >.999 | 0 | 3 (3.66) | >.999 | 0 | 3 (5.66) | .266 |
| Flare during pregnancy | 8 (80.00) | 29 (36.25) | .008 | 5 (62.50) | 32 (39.02) | .198 | | | |

* number of positive tests/number tested.

† excluding hydroxychloroquine, −6 M = 6 months prior to conception, ACR = American College of Rheumatology, ACL/LAC = anti-cardiolipin antibodies/lupus anti-coagulants, APS = anti-phospholipid syndrome, SDI = Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index, SLEDAI-2K = systemic lupus erythematosus disease activity index – 2000.

**Table 4**

**Univariable analysis and multiple logistic regression analysis of factors associated with adverse fetal outcomes in pregnant SLE patients.**

| | | Pregnancy loss | | | | Prematurity | | | Small for gestational age | | | Low birth weight | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **N1** | **n** | **OR (95% CI)** | ***P* value** | **N2** | **n** | **OR (95% CI)** | ***P* value** | **n** | **OR (95% CI)** | ***P* value** | **n** | **OR (95% CI)** | ***P* value** |
| Age at pregnancy | | | | | | | | | | | | | | |
| <25 years | 39 | 4 | 3.64 | | 35 | 21 | 0.93 | | 13 | 0.34 | | 19 | 0.84 | |
| ≥25 years | 51 | 15 | (1.01–16.37) | .027[a] | 36 | 21 | (0.32–2.67) | .886 | 6 | (0.09–1.16) | .051 | 18 | (0.30–2.37) | .718 |
| Disease duration prior to conception | | | | | | | | | | | | | | |
| <5 years | 56 | 8 | 2.87 | | 48 | 28 | 1.11 | | 13 | 0.95 | | 26 | 0.78 | |
| ≥5 years | 34 | 11 | (0.90–9.34) | .042 | 23 | 14 | (0.36–3.52) | .839 | 6 | (0.25–3.28) | .929 | 11 | (0.25–2.36) | .617 |
| Hypertension | | | | | | | | | | | | | | |
| No | 67 | 12 | 2.00 | | 55 | 33 | 0.86 | | 12 | 2.79 | | 27 | 1.73 | |
| Yes | 23 | 7 | (0.56–6.64) | .204 | 16 | 9 | (0.24–3.15) | .788 | 7 | (0.71–10.44) | .081 | 10 | (0.48–6.59) | .345 |
| Previous pregnancy | | | | | | | | | | | | | | |
| 0 | 45 | 7 | 1.97 | | 38 | 21 | 1.42 | | 11 | 0.78 | | 21 | 0.76 | |
| ≥1 | 45 | 12 | (0.62–6.61) | .196 | 33 | 21 | (0.49–4.12) | .474 | 8 | (0.23–2.56) | .655 | 16 | (0.27–2.15) | .568 |
| Pregnancy loss (ever) | | | | | | | | | | | | | | |
| No | 58 | 10 | 1.88 | | 48 | 30 | 0.65 | | 13 | 0.95 | | 26 | 0.78 | |
| Yes | 32 | 9 | (0.58–5.92) | .226 | 23 | 12 | (0.21–2.03) | .408 | 6 | (0.25–3.28) | .929 | 11 | (0.25–2.36) | .617 |
| Renal disorder (ever) | | | | | | | | | | | | | | |
| No | 18 | 1 | 5.67 | | 17 | 6 | 3.67 | | 3 | 1.96 | | 5 | 3.49 | |
| Yes | 72 | 18 | (0.76–249.73) | .071[b] | 54 | 36 | (1.02–13.92) | .022 | 16 | (0.45–12.00) | .330 | 32 | (0.96–14.27) | .032 |
| SLE disease activity at conception | | | | | | | | | | | | | | |
| Remission and mild | 79 | 15 | 2.44 | | 64 | 38 | 0.91 | | 16 | 2.25 | | 33 | 1.25 | |
| Moderate and high | 11 | 4 | (0.46–11.06) | .186 | 7 | 4 | (0.14–6.76) | .909 | 3 | (0.29–14.72) | .311 | 4 | (0.19–9.22) | .779 |
| Prednisolone >10 mg/day at conception | | | | | | | | | | | | | | |
| No | 74 | 13 | 2.82 | | 61 | 36 | 1.04 | | 14 | 3.36 | | 31 | 1.45 | |
| Yes | 16 | 6 | (0.70–10.38) | .076[c] | 10 | 6 | (0.22–5.55) | .953 | 5 | (0.66–16.66) | .073 | 6 | (0.31–7.68) | .590 |
| IM drugs used at conception | | | | | | | | | | | | | | |
| No | 68 | 15 | 0.78 | | 53 | 32 | 0.82 | | 14 | 1.07 | | 25 | 2.24 | |
| Yes | 22 | 4 | (0.17–2.93) | .699 | 18 | 10 | (0.24–2.83) | .719 | 5 | (0.25–3.99) | .910 | 12 | (0.65–8.33) | .152 |
| Prednisolone >10 mg/day and IM drugs used at conception | | | | | | | | | | | | | | |
| No | 82 | 17 | 1.27 | | 65 | 40 | 0.31 | | 17 | 1.41 | | 34 | 0.91 | |
| Yes | 8 | 2 | (0.12–7.98) | .778 | 6 | 2 | (0.03–2.40) | .179[d] | 2 | (0.12–10.86) | .704 | 3 | (0.11–7.33) | .914 |
| HCQ used during pregnancy | | | | | | | | | | | | | | |
| No | 47 | 11 | 0.75 | | 36 | 23 | 0.67 | | 11 | 0.67 | | 21 | 0.60 | |
| Yes | 43 | 8 | (0.23–2.33) | .577 | 35 | 19 | (0.23–1.93) | .410 | 8 | (0.20–2.20) | .464 | 16 | (0.21–1.70) | .287 |
| Organ involvement during Pregnancy | | | | | | | | | | | | | | |
| Cutaneous vasculitis | | | | | | | | | | | | | | |
| No | 87 | 18 | 1.92 | | 69 | 41 | 0.68 | | 18 | 2.83 | | 36 | 0.92 | |
| Yes | 3 | 1 | (0.03–38.45) | .598 | 2 | 1 | (0.01–55.50) | .789 | 1 | (0.03–226.66) | .451 | 1 | (0.01–74.11) | .952 |
| Arthritis | | | | | | | | | | | | | | |
| No | 88 | 19 | 0.71 | | 69 | 40 | 3.64 | | 19 | 0.52 | | 36 | 0.92 | |
| Yes | 2 | 0 | (0.03–15.47) | .829 | 2 | 2 | (0.17–78.70) | .410 | 0 | (0.02–11.28) | .676 | 1 | (0.01–74.11) | .952 |
| Renal | | | | | | | | | | | | | | |
| No | 50 | 9 | 1.52 | | 41 | 19 | 3.80 | | 6 | 4.46 | | 13 | 8.62 | |
| Yes | 40 | 10 | (0.48–4.78) | .419 | 30 | 23 | (1.21–12.72) | .010[e] | 13 | (1.28–16.62) | .007[f] | 24 | (2.54–31.31) | <.001[g] |
| Mucocutaneous | | | | | | | | | | | | | | |
| No | 63 | 15 | 0.56 | | 48 | 30 | 0.65 | | 15 | 0.46 | | 28 | 0.46 | |
| Yes | 27 | 4 | (0.12–2.03) | .338 | 23 | 12 | (0.21–2.03) | .408 | 4 | (0.10–1.76) | .217 | 9 | (0.14–1.42) | .130 |
| Hematologic | | | | | | | | | | | | | | |
| No | 82 | 19 | 0.19 | | 63 | 36 | 2.25 | | 15 | 3.20 | | 32 | 1.61 | |
| Yes | 8 | 0 | (0.01–3.47) | .264 | 8 | 6 | (0.36–24.23) | .333 | 4 | (0.52–19.11) | .115 | 5 | (0.28–11.21) | .532 |
| Flares during pregnancy | | | | | | | | | | | | | | |
| No | 53 | 14 | 0.44 | | 39 | 19 | 2.69 | | 8 | 2.03 | | 15 | 3.52 | |
| Yes | 37 | 5 | (0.11–1.47) | .140 | 32 | 23 | (0.90–8.28) | .048 | 11 | (0.62–6.84) | .189 | 22 | (1.18–10.70) | .011 |

[a] AOR (95% CI) = 4.15 (1.10–15.72), *P* = .036.
[b] AOR (95% CI) = 9.21 (1.03–82.51), *P* = .047.
[c] AOR (95% CI) = 3.89 (0.99–15.20), *P* = .051.
[d] AOR (95% CI) = 0.11 (0.02–0.85), *P* = .034.
[e] AOR (95% CI) = 6.0 (1.77–20.52), *P* = .004.
[f] AOR (95% CI) = 4.46 (1.44–13.78), *P* = .009.
[g] AOR (95% CI) = 10.01 (3.07–32.62), *P* < .001.

HCQ = hydroxychloroquine, IM drugs = immunosuppressive drugs, excluding HCQ, n = number of pregnancies with positive conditions, N1 = number of pregnancies, N2 = number of pregnancies with live births.

**Table 5**

**Univariable analysis and multiple logistic regression analysis of factors associated with adverse maternal outcomes in pregnant SLE patients.**

| | | Premature rupture of the membrane | | | | Pregnancy induced hypertension | | | | Flares | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Characteristics** | **N** | **n** | **OR** | **95% CI** | ***P* value** | **n** | **OR** | **95% CI** | ***P* value** | **n** | **OR** | **95% CI** | ***P* value** |
| Age at pregnancy | | | | | | | | | | | | | |
| <25 years | 39 | 2 | Ref. | | | 4 | Ref. | | | 18 | Ref. | | |
| ≥25 years | 51 | 8 | 3.44 | 0.62–34.83 | .114 | 4 | 0.74 | 0.13–4.31 | .690 | 19 | 0.69 | (0.27–1.76) | .395 |
| Disease duration prior to conception | | | | | | | | | | | | | |
| <5 years | 56 | 7 | Ref. | | | 6 | Ref. | | | 22 | Ref. | | |
| ≥5 years | 34 | 3 | 0.68 | 0.10–3.25 | .590 | 2 | 0.52 | 0.05–3.17 | .435 | 15 | 1.22 | (0.47–3.15) | .652 |
| Hypertension | | | | | | | | | | | | | |
| No | 67 | 9 | Ref. | | | 7 | Ref. | | | 23 | Ref. | | |
| Yes | 23 | 1 | 0.29 | 0.01–2.36 | .232 | 1 | 0.39 | 0.01–3.35 | .375 | 14 | 2.98 | (1.01–8.99) | .026 |
| Previous pregnancy | | | | | | | | | | | | | |
| 0 | 45 | 4 | Ref. | | | 4 | Ref. | | | 20 | Ref. | | |
| ≥1 | 45 | 6 | 1.58 | 0.34–8.16 | .502 | 4 | 1.00 | 0.17–5.76 | >.999 | 17 | 0.76 | (0.30–1.91) | .520 |
| Pregnancy loss (ever) | | | | | | | | | | | | | |
| No | 58 | 7 | Ref. | | | 6 | Ref. | | | 28 | Ref. | | |
| Yes | 32 | 3 | 0.75 | 0.12–3.63 | .697 | 2 | 0.58 | 0.05–3.52 | .514 | 9 | 0.42 | (0.14–1.15) | .063 |
| Renal disorder (ever) | | | | | | | | | | | | | |
| No | 18 | 1 | Ref. | | | 0 | Ref. | | | 5 | Ref. | | |
| Yes | 72 | 9 | 2.43 | 0.30–112.60 | .402 | 8 | 4.88 | 0.27–88.50 | .284 | 32 | 2.08 | (0.61–8.19) | .199 |
| SLE disease activity at conception | | | | | | | | | | | | | |
| Remission and mild | 79 | 10 | Ref. | | | 7 | Ref. | | | 32 | Ref. | | |
| Moderate and high | 11 | 0 | 0.29 | 0.02–5.26 | .401 | 1 | 1.03 | 0.02–9.54 | .980 | 5 | 1.22 | (0.27–5.27) | .755 |
| Prednisolone >10 mg/day at conception | | | | | | | | | | | | | |
| No | 74 | 10 | Ref. | | | 7 | Ref. | | | 32 | Ref. | | |
| Yes | 16 | 0 | 0.19 | 0.01–3.34 | .254 | 1 | 0.64 | 0.01–5.64 | .682 | 5 | 0.60 | (0.15–2.11) | .377 |
| IM drugs used at conception | | | | | | | | | | | | | |
| No | 68 | 8 | Ref. | | | 8 | Ref. | | | 30 | Ref. | | |
| Yes | 22 | 2 | 0.75 | 0.07–4.22 | .729 | 0 | 0.16 | 0.01–2.85 | .212 | 7 | 0.59 | (0.18–1.79) | .308 |
| Prednisolone >10 mg/day **and** IM drugs used at conception | | | | | | | | | | | | | |
| No | 82 | 10 | Ref. | | | 8 | Ref. | | | 36 | Ref. | | |
| Yes | 8 | 0 | 0.41 | 0.02–7.57 | .546 | 0 | 0.52 | 0.03–9.74 | .659 | 1 | 0.18 | (0.00–1.55) | **.085**[c] |
| HCQ used during pregnancy | | | | | | | | | | | | | |
| No | 47 | 8 | Ref. | | | 5 | Ref. | | | 20 | Ref. | | |
| Yes | 43 | 2 | 0.24 | 0.02–1.31 | .062 | 3 | 0.63 | 0.09–3.50 | .542 | 17 | 0.88 | (0.35–2.22) | .771 |
| Organ involvement during pregnancy | | | | | | | | | | | | | |
| Cutaneous vasculitis | | | | | | | | | | | | | |
| No | 87 | 10 | Ref. | | | 8 | Ref. | | | 34 | Ref. | | |
| Yes | 3 | 0 | 1.05 | 0.05–21.88 | .973 | 0 | 1.34 | 0.06–28.11 | .852 | 3 | 10.86 | (0.54–216.71) | .119[d] |
| Arthritis | | | | | | | | | | | | | |
| No | 88 | 10 | Ref. | | | 8 | Ref. | | | 36 | Ref. | | |
| Yes | 2 | 0 | 1.50 | 0.07–33.32 | .799 | 0 | 1.89 | 0.08–42.79 | .688 | 1 | 1.44 | (0.02–115.53) | .796 |
| Renal | | | | | | | | | | | | | |
| No | 50 | 4 | Ref. | | | 3 | Ref. | | | 10 | Ref. | | |
| Yes | 40 | 6 | 2.03 | 0.44–10.49 | .294 | 5 | 2.24 | 0.40–15.24 | .282 | 27 | 8.31 | (2.90–24.34) | <.001[e] |
| Mucocutaneous | | | | | | | | | | | | | |
| No | 63 | 6 | Ref. | | | 4 | Ref. | | | 20 | Ref. | | |
| Yes | 27 | 4 | 1.65 | 0.31–7.69 | .464 | 4 | 2.56 | 0.43–14.84 | .196 | 17 | 3.66 | (1.29–10.54) | .006[f] |
| Hematologic | | | | | | | | | | | | | |
| No | 82 | 8 | Ref. | | | 5 | Ref. | | | 29 | Ref. | | |
| Yes | 8 | 2 | 3.08 | 0.26–21.22 | .190 | 3 | 9.24 | 1.07–64.46 | .003[b] | 8 | 30.83 | (1.72–553.28) | .020[g] |
| Flares during pregnancy | | | | | | | | | | | | | |
| No | 53 | 2 | Ref. | | | 3 | Ref. | | | | | | |
| Yes | 37 | 8 | 7.03 | 1.26–70.80 | .008[a] | 5 | 2.60 | 0.46–17.73 | .198 | | | | |

[a] AOR (95% CI) = 8.45 (1.58–45.30), *P* = .013.
[b] AOR (95% CI) = 9.24 (1.70–50.24), *P* = .010.
[c] AOR (95% CI) = 0.08 (0.01–0.68), *P* = .021.
[d] AOR (95% CI) = 33.87 (1.05–1,094.65), *P* = .047.
[e] AOR (95% CI) = 31.89 (6.66–152.69), *P* < .001.
[f] AOR (95% CI) = 9.17 (1.83–45.90), *P* = .007.
[g] AOR (95% CI) = 128.00 (4.60–3564.46), *P* = .004.
HCQ = hydroxychloroquine, IM drugs = immunosuppressive drugs, excluded HCQ, n = number of pregnancies with positive conditions, N1 = number of pregnancies, N2 = number of pregnancies with live birth.

4.15 [1.10–15.72], $P = .036$), and ever having renal involvement (9.21 [1.03–82.51], $P = .047$). Prednisolone used (>10 mg/day) at conception almost reached a predicting factor for fetal loss (3.89 [0.99–15.20], $P = .051$). Renal involvement during pregnancy independently predicted prematurity (6.02 [1.77–20.52], $P = .004$), and SGA (4.46 [1.44–13.78], $P = .009$) and LBW infants (10.01 [3.07–32.62], $P < .001$). Prednisolone (>10 mg/day) and immunosuppressive drugs used at conception independently reduced the risk of prematurity (0.11 [0.02–0.85], $P = .034$). SLE flares and hematologic involvement during pregnancy independently predicted PROM (8.45 [1.58–45.30], $P = .013$) and PIH (9.24 [1.70–50.24], $P = .010$), respectively. Independent predicting factors for SLE flares during pregnancy included the presence of cutaneous vasculitis (AOR [95% CI]) 33.87 [1.05–1094.65], $P = .047$), and renal (31.89 [6.66–152.69], $P < .001$), mucocutaneous (9.17 [1.83–45.90], $P = .007$) and hematologic involvement (128.00 [4.60–3,564.46], $P = .004$). Prednisolone (>10 mg/day) and immunosuppressive drugs used at conception independently reduced the risk of SLE flares during pregnancy (0.08 [0.01–0.68, $P = .021$).

## 4. Discussion

Despite significant improvement in medical care for pregnant SLE patients, their APOs are still a significant issue.[5,18] Fetal loss (both spontaneous abortion and intra-uterine death), pre-term birth, intra-uterine growth retardation, SGA and LBW in the fetus, and PIH, pre-eclampsia/eclampsia and flares in the mother are among the major APOs of concern. Reports on SLE patients with APOs varied greatly among studies. This could be explain partly by the difference in time period of the study and ethnicity and socioeconomic status of the patients, as well as SLE disease activity prior to and at the time of conception, organ involvement at conception, rate and organ of flares, and prevalence of ACL/LAC or anti-phospholipid syndrome in the population studied.[1,3,19]

Progressive improvement in pregnancy outcomes over a 25-year period was observed in this study. The proportion of successful pregnancies tended to improve with an increased proportion of full-term births and decreased proportion of pre-term infants. An increased proportion of infants with SGA and LBW had slightly decreased mean fetal birth weight; although all of these changes did not reach statistical significance. The improvement in pregnancy outcomes in Thai SLE patients was similar overtime to that in many previous reports.[5,18,20,21] However, the reason for the increased frequency of SGA and LBW was not clear, despite more frequent full-term birth infants.

This study also found that pregnancy outcomes of subsequent pregnancies in SLE patients showed a slightly decreased proportion of live births, full-term births, and SGA and LBW infants, but with slightly increased proportion of fetal loss, particularly among medical terminations. The lower proportion of SGA and LBW in the subsequent pregnancies in this study was similar to that of Wallanius et al,[22] but different from that of Korese et al,[23] who found that the fetal and maternal outcomes were almost similar between the first and subsequent pregnancies, except for the latter having slightly lower pre-term births. Reasons for the higher proportion of medical terminations in subsequent pregnancies in this study were not clear, but this might have been due to decisions made by the mothers and physicians, who were afraid of severe maternal or fetal complications if the pregnancy continued, and the patients probably had a baby already from the previous pregnancy. The proportion of cesarean section delivery among the subsequent pregnancies in this study was significantly (approximately 2 times) higher than that in the first pregnancy, which was similar to that reported by Wallenius et al.[22] This could be explained by the perception of the patients and physicians in that they were afraid of possible uterine rupture during delivery.

The PIH and eclampsia prevalence of 8.89% and 1.11%, respectively, in this study was in line with many previous reports that showed prevalence of 0–19% and 0–20% for PIH[20,23–27] and pre-eclampsia, respectively[20,23–27]. However, when looking at details, studies with a high incidence of PIH had a rather low incidence of pre-eclampsia or vise-versa; except for that reported by Wu et al,[27] and Kroese et al.[23] The reason for the discordance among these reports was unclear. It is not easy in clinical practice to differentiate between PIH and pre-eclampsia in pregnant patients with pre-existing hypertension and renal disease, as hypertension is an important clinical feature in both conditions. For example, a patient with pre-existing hypertension and some degree of proteinuria has slightly increasing proteinuria (without blood cells or cellular casts in the urine, with decreasing complement level, or increasing anti-dsDNA), and elevated blood pressure in the late course of pregnancy. In this situation, many physicians might consider PIH, while others consider pre-eclampsia. A definite diagnosis of these 2 conditions probably can be made only upon patient follow-up of the patients whether both hypertension and proteinuria are resolved or returned to baseline level prior to the development of hypertension and increasing proteinuria during the post-partum period. There were no pre-eclampsia cases in this study. As patients with increasing hypertension and slightly increasing proteinuria without active urine sediment had their blood pressure, but not the proteinuria, returned to normal or baseline during the post-partum period. These patients were considered to have PIH and not pre-eclampsia.

Similar to the differentiation between PIH and pre-eclampsia, differentiation between pre-eclampsia and active nephritis flare is another challenging issue in clinical practice. Several reviews suggest that the presence of extra-renal manifestation, past history of lupus nephritis, presence of or increasing proteinuria at the early trimester of pregnancy, presence of new hypertension onset, presence of active urinary sediments, decreasing serum complement levels, increasing anti-dsDNA levels and normal serum uric acid, favor active nephritis. However, if the aforementioned conditions occur late in the pregnancy, and the patient does not have decreasing complement or increasing anti-dsDNA levels, differential diagnosis between active nephritis and pre-eclampsia would be more difficult.[28–30] The situation would be more complicated if the patient has underlying hypertension prior to pregnancy or slight proteinuria prior to conception. Furthermore, these 2 conditions can co-exist in the same patients.[31] Some authors have suggested performing a kidney biopsy in the latter condition,[29,32] as the management of active lupus nephritis and pre-eclampsia is different. Again, sometimes the diagnosis can be made only upon delivery of the fetus when the above conditions disappear or return to normal.[3] All of the patients who had significantly increasing proteinuria in this study also had active urine sediment, and the degree of proteinuria did not return to normal or baseline at the end of the post-partum period. All of them also showed renal response to an increasing dose of corticosteroid and immunosuppressive drugs, therefore, they were more likely to have active nephritis flare rather than pre-eclampsia.

The pathogenic mechanisms of PIH and pre-eclampsia are not clear, but have been reviewed widely, and included innate

immunity,[33] bioactive factors (such as inflammatory cytokines, angiogenetic factors, growth factors, etc.),[34,35] oxidative stress,[36] placental vascular maladaptation,[37] and endothelial dysfunction.[38,39] Among these, endothelial dysfunction is the most likely underlying mechanism,[39] which causes imbalance between an endothelial-derived vasodilator (such as nitric oxide and prostacyclin) and vasoconstrictors (such as endothelin-1, thromboxane A2), leading to the promotion of vasoconstriction, hypertension, and pre-eclampsia. Placenta ischemia stimulates the release of several bioactive factors and inflammatory cytokines that target the endothelial cells that lead to generalized endothelial cell dysfunction, which in turn causes vascular remodeling, increased arterial stiffness, and hypertension. Current treatment options of pre-eclampsia are limited. Only low dose aspirin has been shown as effective and is recommended by several international obstetrics and gynecologists guidelines for use in preventing pre-eclampsia in high risk patients.[40] Unfortunately, the effect of low dose aspirin on pregnancy outcomes was not determined in this study.

The effect of HCQ use on pregnancy outcomes also has been of interest in lupus pregnancy, although many previous studies could not find a significant difference in overall SLE pregnancy outcomes between HCQ users and non-users.[41–43] However, some studies showed some beneficial effects of HCQ use during pregnancy, including lower rate of fetal loss and pre-term births,[20,44] intra-uterine growth restriction (IUGR) in the fetus,[44] longer duration of pregnancy,[42] flare prevention,[43,45] and decreased PIH.[46] Although no significant difference in APOs among HCQ users and non-users was demonstrated in this study, there tended to be fewer maternal complications among HCQ users, particularly in a lower proportion of PROM, PIH and SLE flares.

Several factors have been identified in association with APOs in pregnant patients with SLE. These have included the presence of renal involvement or active nephritis,[20,24,47–53] SLE flares during pregnancy,[7,24,50,53,54] active disease prior to or during pregnancy,[20,50,54–56] hypertension,[7,24,25,54–57] presence of anti-phospholipid antibodies (APL) and/or lupus anti-coagulants,[7,20,23,24,50,53,54,56,57] cytopenia,[41,50,52,54] and hypocomplementemia.[20,25,50,54,56,58,59] This study also confirmed that renal involvement during pregnancy was associated with poor pregnancy outcomes, in both the fetus and mother. However, the presence of hypertension only associated with maternal flares.

Although APOs have been reported in several studies, only a few identified independent predicting factors for adverse fetal and maternal outcomes. In addition, the results of these predicting factors also were inconsistent. For example, Cortes-Hernandez et al[25] found that the presence of ACL and hypertension during pregnancy were independent predicting factors for poor fetal outcomes, whereas the presence of anti-β2-glycoprotein-1, hypertension at conception and hypocomplemetemia were independent predicting factors for fetal loss. Kwok et al[24] found that hypertension was an independent predicting factor for fetal loss, nephritis for SGA, low serum albumin for IUGR and SLE flares for prematurity among infants; and nephritis was an independent predicting factor for SLE flares, and hypertension and high disease activity for pre-eclampsia among mothers. Ko et al[26] found that the presence of APL antibodies was an independent predicting factor for fetal loss and pre-term births, and active disease for pre-term births. Active SLE and SLE flares were independent predicting factors for PIH and IUGR among mothers. Buyon et al[41] found that the presence of LAC, hypertension, high disease activity, maternal flares, and thrombocytopenia were predictors of APOs. Lui et al[60] found that pre-eclampsia/eclampsia and thrombocytopenia were independent predicting factors for fetal loss and SLE flares in mothers. Pre-eclampsia/eclampsia also was an independent predicting factor for pre-term birth among infants. Borella et al[56] found that hypertension was an independent predicting factor for fetal loss, miscarriage and SGA, and anti-phospholipid syndrome (APS) for prematurity in infants; whereas LAC was an independent predicting factor for pre-eclampsia, and active disease at −6 M for PROM. Kalok et al[6] found that SLE flares and active disease were predicting factors for fetal loss and pre-term birth, and also SLE flares for SGA among infants. Active SLE was an independent predicting factor for SLE flares and lupus nephritis, while SLE flares and the presence of APL antibodies were independent predicting factors for pre-eclampsia among mothers. Wu et al[59] recently found that unplanned pregnancy, hypocomplementemia and urine protein >1.0 gm/day were independent predicting factors for fetal loss. This study found that age >25 years and ever having renal involvement were independent predicting factors for fetal loss, renal involvement during pregnancy, prematurity, SGA and LBW among infants. SLE flare during pregnancy and hematologic involvement were independent predicting factors for PROM and PIH, respectively, among mothers. It was interesting that the use of prednisolone (>10 mg/day) and immunosuppressive drugs at conception was an independent protecting factor for prematurity. The presence of cutaneous vasculitis, and renal, mucocutaneous and hematologic involvement during pregnancy was an independent predicting factor for SLE flares; while the use of prednisolone (>10 mg/day) and immunosuppressive drugs at the time of conception reduced the risk of SLE flares independently. The predicting factors identified from this study were similar to many of those mentioned in the aforementioned studies. However, this study could not demonstrate that the presence of ACL/LAC was an independent factor for poor pregnancy outcomes. This might relate to the small number of patients with poor pregnancy outcome, who were among those with a positive test for these antibodies, as previously discussed. A larger study, including more patients with APL/LAC, needs to be carried out in order to verify this association in Thai patients.

The use of mSLEDAI-2K, the modified SFI and modified SLE disease activity severity score would have caused a limitation in this study. The SLE disease activity or flares would be underestimated (as the score for anti-dsDNA and complement would not be counted), making it difficult to compare this study with those that used scores from the original version. However, the mSLEDAI-2K has been shown to correlate very well ($r$ = 0.924) with the original SLEDAI-2K.[13] In addition, use of the mSLEDAI-2K score in this study reflects real world practice, as many institutions could not perform anti-dsDNA and complements routinely. The small number of patients with positive ACL/LAC did not demonstrate the effect of these antibodies on APOs clearly. However, all of the patients in this study were taken care of by the same group of rheumatologists, who collectively made more uniformed therapeutic decisions, which should add more strength to the outcomes.

## 5. Conclusion

This study showed that pregnancy outcomes in Thai patients with SLE has improved over a 25-year period. However, a significant

number of APOs were still observed. Renal involvement and flares during pregnancy were associated with both poor fetal and maternal outcomes. The beneficial effect of HCQ in lupus pregnancy was not demonstrated clearly, but there was a trend in favor of better pregnancy outcomes among the HCQ users. Age ≥ 25 years at conception, the presence of or ever having renal involvement during pregnancy, presence of SLE flare and hematologic involvement during pregnancy were predicting factors for poor pregnancy outcomes. Cutaneous vasculitis, and renal, hematologic and mucocutaneous involvement during pregnancy predicted SLE flare. The effect of APL/LAC on pregnancy outcomes in Thai populations needs further investigations.

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