Arch Rheumatol 2022;37(3):361-374
doi: 10.46497/ArchRheumatol.2022.9140

ORIGINAL ARTICLE

Pregnancy outcomes between pregnant systemic lupus erythematosus patients with clinical remission and those with low disease activity: A comparative study

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ABSTRACT

Objectives: This study aims to compare pregnancy outcomes between systemic lupus erythematosus (SLE) patients who attained clinical remission based on the Definition of Remission in SLE (DORIS) and those with lupus low disease activity based on Low Lupus Disease Activity State (LLDAS).

Patients and methods: Between January 1993 and June 2017, a total of 90 pregnancies (one twin pregnancy) from 77 patients (mean age: 26.9±4.8 years; range, 17.9 to 37.3 years) were included in the study. The clinical remission and the LLDAS groups were modified into modified clinical remission and LLDAS groups, respectively by omitting Physician Global Assessment (PGA). The clinical SLE disease activity index (cSLEDAI) score was used for LLDAS.

Results: Pregnancies in 49 patients occurred, when they were in modified clinical remission and in 57 in modified LLDAS. There was no significant difference in demographic characteristics, disease activity, or medication received at conception between the two groups. Pregnancy outcomes were similar between the modified clinical remission and the modified LLDAS groups in terms of successful pregnancy (83.67% *vs.* 84.21%), full-term births (38.78% *vs.* 38.60%), fetal losses (16.33% *vs.* 15.79%), spontaneous abortions (14.29% *vs.* 14.04%), small for gestational age infants (18.37% *vs.* 19.30%), low birth weight infants (42.86% *vs.* 40.35%), maternal complications (46.94% *vs.* 49.12%), and maternal flares (36.73% *vs.* 40.35%). The agreement of pregnancy outcomes was very high between the two groups (91.11% agreement).

Conclusion: Pregnancy outcomes in SLE patients who achieved modified clinical remission and modified LLDAS were comparable.

Keywords: Low disease activity, pregnancy, pregnancy outcome, remission, systemic lupus erythematosus.

Pregnancy in systemic lupus erythematosus (SLE) patients is challenging in clinical practice, as it often associates with increased poor pregnancy outcomes.[1-4] Pregnant SLE patients have a reportedly higher rate of maternal and fetal complications. 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 the mother and fetus.[5,6] Several factors have been found to be associated with poor pregnancy outcomes, including ethnicity and socioeconomic status, SLE disease activity before and at the time of conception, organ involvement at conception, rate and organ of flares, and prevalence of anti-phospholipid antibodies, lupus anticoagulants (LAC) or the presence of anti-phospholipid syndrome (APS).[1,5,7,8] Therefore, pregnancy should be planned for SLE patients. It is usually accepted that both maternal and fetal outcome are best, if SLE patients have been in remission

Received: August 02, 2021 ***Accepted:*** October 11, 2021 ***Published online:*** December 24, 2021

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Citation:
Louthrenoo W, Trongkamolthum T, Kasitanon N, Wongthanee A. Pregnancy outcomes between pregnant systemic lupus erythematosus patients with clinical remission and those with low disease activity: A comparative study. Arch Rheumatol 2022;37(3):361-374.

for at least six months prior to conception (-6M); but if this is not possible, the patients should have had stable low disease activity and no severe active disease involving the heart, lungs, kidneys and central nervous system within the previous six months.[5,6]

Although remission has been suggested as a target treatment for SLE patients, no clear definition has existed. An international task force on definitions of remission in SLE (DORIS) recently developed a remission framework,[9,10] which classifies remission in SLE into two groups: complete remission (serology and complements must be negative or normal) and clinical remission (serology and complements not included). These two groups of remission are classified further into two subgroups according to the treatment received (with or without treatment). Unfortunately, studies have shown that complete remission is rare in clinical practice, but clinical remission can be more achievable.[10,11] The recently developed Lupus Low Disease Activity State (LLDAS)[12] has shown that patients achieving it have less organ damage accrual and better quality of life.[11-13] As the LLDAS is a less stringent treatment target than remission, its use as an outcome in SLE has been suggested.[12]

Several studies have shown that pregnancy in SLE patients with high disease activity (or not attaining low disease activity) was associated with poor pregnancy outcomes.[8,14-16] However, to the best of our knowledge, a direct comparison in pregnancy outcomes between pregnant SLE patients who attain clinical remission and those with low disease activity has never been determined. Therefore, in the present study, we aimed to compare pregnancy outcomes and agreement between pregnant SLE patients who achieved clinical remission and those with low disease activity at the time of conception. In addition, pregnancy outcomes were compared between pregnant SLE patients who achieved modified clinical remission or modified low disease activity and their counterparts who did not.

PATIENTS AND METHODS

This comparative study was conducted at Chiang Mai University, Faculty of Medicine, Department of Internal Medicine between January 1993 and June 2017. Medical records of pregnant SLE patients in the Chiang Mai University lupus cohort were reviewed. The diagnosis of SLE was made according to the 1997 update of the American College of Rheumatology (ACR) revised criteria for the classification of SLE.[17] Only pregnant SLE patients, who had completed their peri-partum care (from the time of pregnancy being documented to the post-partum period [six weeks after termination of pregnancy or delivery]) in our center were included in this study. The cohort comprised a total of 1,167 female patients. However, 90 pregnancies (one twin pregnancy) from 77 patients (mean age: 26.9±4.8 years; range, 17.9 to 37.3 years) were eligible for the study.

Patients in the cohort usually were followed regularly at one- to three-month intervals, depending on SLE disease activity or other clinical encounters. The clinical and laboratory findings and SLE treatment were captured at -6M and three months prior to conception (-3M), at the time of conception, at each trimester, and during the post-partum period. Complete blood counts, urine analysis, and renal and liver functions were recorded routinely. The 24-h urine protein creatinine ratio (urine protein in g/day to urine creatinine in g/day) was determined only in nephritis cases (urine protein >0.5 g/day). Data on the presence of anti-cardiolipin antibodies (ACL) and LAC also were recorded. Anti-β2 glycoprotein-1 (anti-β2GP1) was not available at this hospital during the study period. If a patient had more than one pregnancy, each pregnancy was considered separately and counted as an individual case. The definition of fetal outcomes (pregnancy loss, miscarriage or spontaneous abortion, intra-uterine fetal death, medical termination or therapeutic abortion, pre-term delivery, full-term delivery, post-term delivery, neonatal death, small for gestational age, and low birth weight infants) and maternal complications (premature rupture of the membrane, oligohydramnios, pre- or post-partum hemorrhage, pregnancy-induced hypertension, preeclampsia, and eclampsia) followed that of standard references.[18]

According to the practice in this study, SLE patients should have been in stable

low disease activity or in clinical remission (taking prednisolone at ≤10 mg/day with or without anti-malarial medication) for at least 12 months to allow for pregnancy. Those receiving the anti-malarial drugs, azathioprine and cyclosporine, prior to conception could continue them during pregnancy, whereas those receiving methotrexate, cyclophosphamide or mycophenolate mofetil replaced them with azathioprine or cyclosporine immediately the pregnancy was documented. Mild-to-moderate and severe flares usually were treated with prednisolone of up to 0.50 mg/kg/day and 0.50-1.00 mg/kg/day, respectively. Anti-malarial drugs also were given to mild-to-moderate flare cases, and azathioprine and cyclosporine to cases with severe flare. Dosages of anti-malarial and immunosuppressive drugs were used according to standard therapeutic dosage.

SLE disease activity and flare assessment

Th SLE disease activity, organ damage accrual and SLE flares were determined by the clinical Systemic Lupus Erythematosus Disease Activity Index (cSLEDAI),[19] Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index,[20] and Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLE flare index (SFI),[21] respectively. As anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies and complements were not routinely available at this institution, clinical remission (not including serology and complements) according to the DORIS framework was used in this study.[9,10] The LLDAS followed the definition described by Franklyn et al.[12] In addition, Physician Global Assessment (PGA) of disease activity was not captured routinely; clinical remission, LLDAS and SFI were modified to modified clinical remission, modified LLDAS, and modified SFI, respectively, by omitting the PGA. Furthermore, the cSLEDAI was used instead of the original Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) in the LLDAS.[22] The pregnancy data, SLE disease activity, and organ damage of the pregnancy cases were obtained from reviews of available longitudinal data in medical records.

Statistical analysis

Statistical analysis was performed using the STATA version 14.2 software (Stata Corp., TX, USA). As some patients had more than one pregnancy, each one was considered individually for statistical analysis. Continuous variables were presented in mean ± standard deviation (SD) or median (min-max), while categorical variables were presented in number and frequency. To determine the differences between two independent samples of continuous variables, the Student t-test was used for variables with normal distribution, and Wilcoxon rank sum test for non-normal distribution. The chi-square test or Fisher exact test was used to determine associations among the categorical variables, where appropriate. The kappa-statistics were used as a method for assessing agreement among raters. The Mantel-Haenszel method was used to determine the association between an exposure and outcome after being adjusted or taken into account for confounding factors. A p value of <0.05 was considered statistically significant.

RESULTS

Demographics, characteristics, and overall pregnancy outcomes of pregnant SLE patients

Details of the demographics, characteristics and pregnancy outcomes of these patients are summarized in Table 1.[23] In brief, 33 (36.67%) pregnancies were active (cSLEDAI score >0) at conception, and all of them were unplanned. Fifteen (16.67%) pregnancies occurred, while no specific SLE medications were being taken. Pregnancies occurred in six and four patients receiving cyclophosphamide and mycophenolate mofetil, respectively, and these medications were discontinued immediately, or switched to azathioprine or cyclosporine when the pregnancy was documented. Twenty-one (45.65%) and 20 (43.78%) of 46 patients tested positive for anti-Ro/SSA and anti-La/SSB antibodies, respectively. Six of 58 (10.34%) tested positive for ACL or LAC, and three of these patients had APS. One APS patient had a history of recurrent spontaneous abortions prior to diagnosis of SLE. Upon current pregnancy, she was given heparin which resulting in a pre-term delivery. Seventy-one (78.89%) pregnancies were successful, with one neonatal death (1.11%). No infants had congenital anomalies or completed heart block. Maternal

Table 1. Demographics, disease activity, treatment received and pregnancy outcomes in pregnant patients with SLE

	n	%	Mean±SD
Demographics and disease activity			
Age at SLE diagnosis in years			21.6±5.9
Age at pregnancy in years			26.9±4.8
cSLEDAI score			
-6M			1.7±3.2
-3M			2.0±3.8
At conception			1.9±3.4
cSLEDAI score >0 at conception	33	36.67	
SDI score			0.4±0.7
Organ involvement at conception			
Renal	20	22.22	
Mucocutaneous lesions	15	16.67	
Cutaneous vasculitis	2	2.22	
Arthritis	1	1.11	
Hematologic abnormalities	1	1.11	
Co-morbidities			
Hypertension	23	25.56	
Dyslipidemia	8	8.89	
Thalassemia	7	7.78	
Diabetes mellitus	1	1.11	
Others	19	21.11	
Anti-phospholipid syndrome	3	3.33	
Serology			
Anti-nuclear antibodies	*89/†90	98.89	
Anti-dsDNA	*50/†85	58.82	
Anti-Smith (anti-Sm)	*1/†12	8.33	
Anti-cardiolipin (ACL)	*4/†58	6.90	
Lupus coagulants (LAC)	*3/†42	7.14	
Anti-Ro/SSA	*21/†46	45.65	
Anti-La/SSB	*20/†47	42.55	
Treatment received and pregnancy outcomes			
SLE specific medications during pregnancy			
None	15	16.67	
Prednisolone	73	81.11	
Hydroxychloroquine	37	41.11	
Azathioprine	10	11.11	
Cyclosporine	3	3.33	
Mode of delivery			
Vaginal	71	78.89	
Cesarean section	19	21.11	
Fetal outcomes			
Successful pregnancy	71	78.89	
Full-term birth	28	31.11	
Pre-term birth**	42	46.67	
Post-term birth	1	1.11	
LBW infants (<2500 grams)**	38	42.22	
SGA infants	19	26.39	
Fetal losses	19	21.11	
Spontaneous abortion	12	13.33	
Therapeutic abortion	5	5.56	
Dead fetus in the utero	2	2.22	
Maternal outcomes			
Maternal complications***	21	23.33	
PROM	10	11.11	
PIH	8	8.89	
Oligohydramnios	4	4.44	
PPH	2	2.22	
Eclampsia	1	1.11	
Flare	37	41.11	

SD: Standard deviation; SLE: Systemic lupus erythematosus; cSLEDAI: Clinical systemic lupus erythematosus disease activity index; -3M: 3 months prior to conception; -6M: 6 months prior to conception; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; Anti-dsDNA: Anti-double stranded deoxyribonucleic acid; Anti-Ro/SSA: Anti-Sjögren's syndrome-related antigen A; Anti-La/SSB: Anti-Sjögren's syndrome-related antigen B;; LBW: Low birth weight; SGA: Small for gestational age; PROM: Premature rupture of the membrane; PIH: Pregnancy-induced hypertension; PPH: Post-partum hemorrhage; * Number of positive tests; † Number of tested; ** One twin pregnancy; *** Concomitant PROM and oligohydramnios, PROM and PPH, PROM and PIH, and PIH and eclampsia occurred in each one.

complications and SLE flares occurred in 21 (23.33%) and 37 (41.11%) pregnancies, respectively. There were no cases of anti-partum hemorrhage, post-partum endometritis, hemolysis elevated liver enzymes and low platelet count (HELLP) syndrome, preeclampsia or maternal death.

Ninety pregnancies were classified into groups according to DORIS and LLDAS definition as follows: modified clinical remission in 49 (with treatment in 37 and without treatment in 12), non-modified clinical remission in 41, modified LLDAS in 57 and non-modified LLDAS in 33. Demographics and clinical characteristics of these patients are shown in Table 2. No significant differences in clinical characteristics or pregnancy outcomes were seen between patients in modified clinical remission who received and did not receive treatment, except for the mean age at SLE diagnosis, where the former was slightly but significantly lower (21.4±5.3 years *vs.* 25.4±5.4 years, respectively; p=0.029) (data not shown).

Pregnancy outcomes between pregnant patients achieving modified clinical remission and those with modified LLDAS

The demographics and clinical characteristics, and the pregnancy outcomes between pregnant SLE patients achieving modified clinical remission and those with modified LLDAS are shown in Table 2 and Table 3. There was no statistically significant difference in the clinical characteristic between the two groups, except for disease activity at conception in the modified LLDAS group, which was slightly but significantly higher (0.2±0.6 *vs.* 0±0, respectively; p=0.020), due to the working definition. There also was no statistically significant difference in fetal or maternal outcomes among the two groups. The agreement between pregnant patients in these two groups was very high (91.11%, kappa 0.818, p<0.001).

Pregnancy outcomes compared between pregnant patients achieving modified clinical remission or those with modified LLDAS and their counterparts

The demographics and clinical characteristics of patients attaining modified clinical remission or modified LLDAS were compared with those of their counterparts and are shown in Table 2. Several significant differences in demographic characteristics were observed, particularly in the cSLEDAI score, and treatment received for patients with modified clinical remission and modified LLDAS and their counterparts who did not, due mainly to the definition of the groups. Compared to their counterparts, at conception, patients in the modified clinical remission and modified LLDAS groups clearly had significantly less hypertension (14.29% *vs.* 39.02%, respectively; p=0.007 and 17.54% *vs.* 39.39%, respectively; p=0.022) or renal involvement (0% *vs.* 48.78%, respectively; p<0.001 and 0% *vs.* 60.61%, respectively; p<0.001). There was no significant difference in the presence of ACL/LAC between patients in the modified clinical remission or modified LLDAS groups and their counterparts, although the presence of anti-Ro/SSA antibodies was significantly higher in the non-modified LLDAS than the modified LLDAS groups (64.71% *vs.* 34.48%, respectively; p=0.047).

Pregnancy outcomes of patients who attained modified clinical remission and modified LLDAS were compared with their counterparts and are shown in Table 3. Although only mean fetal birth weight was significantly higher in the modified clinical remission group (2,516.17±604.93 g *vs.* 2,170.48±641.91 g, respectively; p=0.020) compared to the non-modified one, other pregnancy outcomes were more favorable in the modified clinical remission group, but without a statistical significance. It was interesting that the proportion of spontaneous abortion and low birth weight infants was similar between the two groups (14.29% *vs.* 12.20% and 42.86% *vs.* 40.48%, respectively). Intra-uterine fetal deaths did not occur in the modified clinical remission group, but two (4.88%) did in the non-modified one. Maternal complications and flares were non-significantly lower in the modified clinical remission group.

Similarly, the mean fetal birth weight and proportion of full-term birth infants were significantly higher in the modified LLDAS group than in their counterparts (2,480.27±612.89 g *vs.* 2,141.46±646.63 g, p=0.033, and 38.60% *vs.* 18.18%, respectively; p=0.044). Other pregnancy outcomes also were more favorable in the modified LLDAS group, but without a statistical significance. The proportion of

Table 2. Demographics and disease activity, and treatment received in pregnant patients with SLE according to the definition of clinical remission and low disease activity

	Modified clinical remission	Modified LLDAS	p1	Non-modified clinical remission	p2	Non-modified LLDAS	p3
Number of pregnancies	49	57		41		33	
Age at SLE diagnosis in years (mean±SD)	22.4±5.6	21.9±5.9	0.658	20.7±6.2	0.19	21.2±6.0	0.599
Disease duration prior to pregnancy in years (mean±SD)	5.1±5.2	5.6±5.6	0.697	5.7±5.1	0.397	4.9±4.1	0.97
Hypertension, n (%)	7 (14.29)	10 (17.54)	0.649	16 (39.02)	0.007	13 (39.39)	0.022
Renal disorder (ever), n (%)	39 (79.59)	46 (80.70)	0.886	33 (80.49)	0.916	26 (78.79)	0.827
Renal involvement at conception, n (%)	0	0		20 (48.78)	<0.001	20 (60.61)	<0.001
Anti-Ro/SSA*, n/N (%)	10/28 (35.71)	10/29 (34.48)	0.922	11/18 (61.11)	0.091	11/17 (64.71)	0.047
Anti-La/SSB*, n/N (%)	10/28 (35.71)	10/29 (34.48)	0.922	10/19 (52.63)	0.250	10/18 (55.56)	0.155
ACL/LAC*, n/N (%)	3/25 (12.00)	4/28 (14.29)	1	3/18 (16.67)	0.683	2/15 (13.33)	1
cSLEDAI score (mean±SD)							
-6M	0.3±1.3	0.3±1.2	0.962	3.4±4.0	<0.001	4.2±4.1	<0.001
-3M	0.0±0.3	0.1±0.4	0.651	4.4±4.7	<0.001	5.5±4.7	<0.001
At conception	0±0	0.2±0.6	0.02	4.2±4.1	<0.001	4.9±4.2	<0.001
SLE specific medications during pregnancy							
Prednisolone, n (%)	36 (73.47)	41 (71.93)	0.859	37 (90.24)	0.043	32 (96.97)	0.003
Dose of prednisolone in mg/day (mean±SD) [min-max]	3.0±2.1 [0-5]	3.1±2.3 [0-7.5]	0.919	15.6±14.0 [0-60]	<0.001	18.5±14.0 [0-60]	<0.001
Hydroxychloroquine, n (%)	20 (40.82)	23 (40.35)	0.961	17 (41.46)	0.95	14 (42.42)	0.847
Immunosuppressive drug, n (%)	8 (16.33)	8 (14.04)	0.742	11 (26.83)	0.224	11 (33.33)	0.031
Azathioprine, n (%)	5 (10.20)	5 (8.77)	0.801	10(24.39)	0.072	10 (30.30)	0.008
Cyclosporine, n (%)	4 (8.16)	4 (7.02)	1.000	1 (2.44)	0.371	1 (3.03)	0.648

LLDAS: Lupus low disease activity state; SLE: Systemic lupus erythematosus; Anti-Ro/SSA: Anti-Sjögren's syndrome-related antigen A;; Anti-La/SSB: Anti-Sjögren's syndrome-related antigen B; ACL: Anti-cardiolipin antibodies; LAC: Lupus anticoagulants; cSLEDAI: Clinical systemic lupus erythematosus disease activity index; -3M: 3 months prior to conception; -6M: 6 months prior to conception; * n/N: Number of positive tests/number of tested; p1: P-value comparing modified clinical remission with modified LLDAS; p2: P-value comparing modified clinical remission with non-modified clinical remission; p3: P-value comparing modified LLDAS with non-modified LLDAS.

Table 3. Pregnancy outcomes in pregnant patients with SLE according to the definition of clinical remission and low disease activity

	Modified clinical remission	Modified LLDAS	p1	Non-modified clinical remission	p2	Non-modified LLDAS	p3
Number of pregnancies	49	57		41*		33*	
Successful pregnancies, n (%)	41 (83.67)	48 (84.21)	0.940	30 (73.17)	0.224	23 (69.70)	0.104
Pregnancy duration in weeks, (mean±SD)	36.22±3.62	36.11±3.50	0.888	35.13±3.49	0.209	35.02±3.73	0.234
Fetal birth weight in grams, (mean±SD)	2,516.17±604.93	2,480.27±612.89	0.782	2,170.48±641.91*	0.022	2,141.46±646.63*	0.033
Fetal outcomes							
Live birth, n (%)	41 (83.67)	48 (84.21)	0.940	31 (73.81)*	0.248	24 (70.59)*	0.122
Term	19 (38.78)	22 (38.60)	0.985	9 (21.95)	0.086	6 (18.18)	0.044
Pre-term	22 (44.90)	26 (45.61)	0.941	21 (50.00)*	0.627	17 (50.00)*	0.685
Post-term	0	0	0	1 (2.44)	0.456	1 (3.03)	0.367
Total fetal loss, n (%)	8 (16.33)	9 (15.79)	0.940	11 (26.33)	0.224	10 (30.30)	0.104
Spontaneous abortion	7 (14.29)	8 (14.04)	0.971	5 (12.20)	0.771	4 (12.12)	0.797
Medical termination or therapeutic abortion	1 (2.04)	1 (1.75)	1.000	4 (9.76)	0.173	4 (12.12)	0.058
Dead fetus in utero	0	0		2 (4.88)	0.205	2 (6.06)	0.132
Neonatal death, n (%)	1 (2.04)	1 (1.75)	1.000	0	1.000	0	1.000
SGA, n (%)	9 (18.37)	11 (19.30)	0.903	10 (24.39)	0.486	8 (24.24)	0.580
LBW (<2500 grams), n (%)	21 (42.86)	23 (40.35)	0.794	17 (40.48)*	0.818	15 (44.12)*	0.724
Maternal complications, n (%)†	23 (46.94)	28 (49.12)	0.822	22 (53.66)	0.525	17 (51.52)	0.827
PROM, n (%)	6 (12.24)	8 (14.04)	0.786	4 (9.76)	0.708	2 (6.06)	0.246
Oligohydramnios, n (%)	2 (4.08)	2 (3.51)	1.000	2 (4.88)	1.000	2 (6.06)	0.622
PPH, n (%)	2 (4.08)	2 (3.51)	1.000	0	0.498	0	0.530
PIH, n (%)	5 (10.20)	6 (10.53)	0.957	3 (7.32)	0.632	2 (6.06)	0.473
Eclampsia, n (%)	1 (2.04)	1 (1.75)	1.000	0	1.000	0	1.000
Flares, n (%)	18 (36.73)	23 (40.35)	0.703	19 (46.34)	0.356	14 (42.42)	0.847
Mild to moderate	4 (22.22)	7 (30.43)	0.556	5 (26.32)	0.772	2 (14.29)	0.267
Severe	14 (77.78)	16 (69.57)		14 (73.68)		12 (85.71)	

LLDAS: Lupus low disease activity state; SD: Standard deviation; SGA: Small for gestational age; LBW: Low birth weight; PROM: Pre-mature rupture of the membrane; PPH: Post-partum hemorrhage; PIH: Pregnancy-induced hypertension; * One twin pregnancy; † Some pregnancies had more than one maternal complication; p1: P-value comparing modified clinical remission with modified LLDAS; p2: P-value comparing modified clinical remission with non-modified clinical remission; p3: P-value comparing modified LLDAS with non-modified LLDAS.

Table 4. Effect of hypertension on pregnancy outcomes in pregnant patients with SLE according to the definition of clinical remission and low disease activity

		Modified clinical remission		*p*	Non-modified clinical remission		*p*	Modified LLDAS		*p*	Non-modified LLDAS		*p*
Number of pregnancies		49			41			57			33		
Hypertension, (n)		No (42)	Yes (7)		No (25)	Yes (16)		No (47)	Yes (10)		No (20)	Yes (13)	
Successful pregnancy, n (%)	Yes	35 (83.33)	6 (85.71)		20 (80.00)	10 (62.50)		39 (82.98)	9 (90.00)		16 (80.00)	7 (53.85)	
	No	7 (16.67)	1 (14.29)		5 (20.00)	6 (37.50)		8 (17.02)	1 (10.00)		4 (20.00)	6 (46.15)	
Odds ratio (95% CI)		1.20 (0.11, 62.97)		0.875	0.42 (0.08, 2.14)		0.217	1.85 (0.20, 90.88)		0.580	0.29 (0.05, 1.75)		0.110
Test for homogeneity				0.437						0.176			
Test for association				0.350						0.379			
Full term birth, n (%)	Yes	16 (38.10)	3 (42.86)		5 (20.00)	4 (25.00)		16 (34.04)	6 (60.00)		5 (25.00)	1 (7.69)	
	No	26 (61.90)	4 (57.14)		20 (80.00)	12 (75.00)		31 (65.96)	4 (40.00)		15 (75.00)	12 (92.31)	
Odds ratio (95% CI)		1.22 (0.16, 8.23)		0.811	1.33 (0.22, 7.58)		0.706	2.91 (0.58, 15.84)		0.126	0.25 (0.01, 2.79)		0.208
Test for homogeneity				0.936						0.069			
Test for association				0.664						0.664			
Pre-term birth, n (%)	Yes	19 (45.24)	3 (42.86)		14 (56.00)	6 (37.50)		23 (48.94)	3 (30.00)		10 (50.00)	6 (46.15)	
	No	23 (54.76)	4 (57.14)		11 (44.00)	10 (62.50)		24 (51.06)	7 (70.00)		10 (50.00)	7 (53.85)	
Odds ratio (95% CI)		0.91 (0.12, 6.12)		0.907	0.47 (0.11, 2.02)		0.248	0.45 (0.07, 2.29)		0.275	0.86 (0.17, 4.29)		0.829
Test for homogeneity				0.534						0.529			
Test for association				0.331						0.358			
Overall maternal complications, n (%)	Yes	18 (42.86)	5 (71.43)		11 (44.00)	11 (68.75)		21 (44.68)	7 (70.00)		8 (40.00)	9 (69.23)	
	No	24 (57.14)	2 (28.57)		14 (56.00)	5 (31.25)		26 (55.32)	3 (30.00)		12 (60.00)	4 (30.77)	
Odds ratio (95% CI)		3.33 (0.47, 37.86)		0.161	2.80(0.63, 13.27)		0.121	2.89 (0.56, 19.09)		0.146	3.38 (0.63, 19.87)		0.101
Test for homogeneity				0.876						0.884			
Test for association				0.039						0.031			
Overall flares, n (%)	Yes	13 (30.95)	5 (71.43)		10 (40.00)	9 (56.25)		16 (34.04)	7 (70.00)		7 (35.00)	7 (53.85)	
	No	29 (69.05)	2 (28.57)		15 (60.00)	7 (43.75)		31 (65.96)	3 (30.00)		13 (65.00)	6 (46.15)	
Odds ratio (95% CI)		5.58 (0.76, 63.33)		0.040	1.93 (0.45, 8.31)		0.309	4.52 (0.86, 29.92)		0.035	2.17 (0.42, 11.35)		0.284
Test for homogeneity				0.339						0.483			
Test for association				0.042						0.026			

LLDAS: Lupus low disease activity state; CI: Confidence interval.

Table 5. Pregnancy outcomes in pregnant patients with SLE, based on the definition of clinical remission and low disease activity, according to period of pregnancy

	Modified clinical remission		Modified LLDAS		p1	Non-modified clinical remission		p2	Non-modified LLDAS		p3
Period of study	n	%	n	%		n	%		n	%	
Number of pregnancies	49		57			41			33		
1993-2001	10/49	20.41	11/57	19.30	0.886	8/41	19.51	0.916	7/33	21.21	0.827
Successful pregnancy	10	100.00	11	100.00		4	50.00	0.023	3	42.86	0.011
Pregnancy loss	0	0	0	0		4	50.00	0.023	4	57.14	0.011
Maternal complication	4	40.00	5	45.45	1.000	6	75.00	0.188	5	71.43	0.367
Maternal flares	3	30.00	4	36.36	1.000	5	62.50	0.342	4	57.14	0.630
2002-2009	13/49	26.53	15	26.32	0.980	12/41	29.27	0.773	10	30.30	0.684
Successful pregnancy	10	76.92	11	73.33	1.000	9	75.00	1.000	8	80.00	1.000
Pregnancy loss	3	23.08	4	26.67	1.000	3	25.00	1.000	2	20.00	1.000
Maternal complication	7	53.85	7	46.67	1.000	5	41.67	0.695	5	50.00	1.000
Maternal flares	6	46.15	6	40.00	1.000	5	41.67	1.000	5	50.00	0.697
2010-2017	26/49	53.06	31	54.39	0.892	21/41	51.22	0.862	16	48.48	0.589
Successful pregnancy	21	80.77	26	83.87	0.759	17	80.95	0.987	12	75.00	0.466
Pregnancy loss	5	19.23	5	16.13	0.759	4	19.05	0.987	4	25.00	0.466
Maternal complication	12	46.15	16	51.61	0.681	11	52.38	0.671	7	43.75	0.609
Maternal flares	9	34.62	13	41.94	0.572	9	42.86	0.563	5	31.25	0.475

LLDAS: Lupus low disease activity state; p1: P-value comparing modified clinical remission with modified LLDAS; p2: P-value comparing modified clinical remission with non-modified clinical remission; p3: P-value comparing modified LLDAS with non-modified LLDAS.

spontaneous abortion and low birth weight infants was similar between the two groups (14.04% *vs.* 12.12% and 40.35% *vs.* 44.12%, respectively). Two fetal deaths in the utero occurred in the non-modified LLDAS group. Maternal complications also were similar between the two groups, but the proportion of severe flare in the modified LLDAS group was lower numerically (69.57% *vs.* 85.71%, respectively; p=0.267) (Table 3).

The effect of hypertension on pregnancy outcomes

As hypertension was significantly different between the modified clinical remission and modified LLDAS groups compared to their counterparts, its effect on pregnancy outcome was determined (Table 4). The proportion of successful pregnancies, and full- and pre-term birth infants was numerically, but not statistically, higher in patients with hypertension in the modified clinical remission or modified LLDAS subgroups than in their counterparts, who did not have hypertension. There also was no association between the presence of hypertension and successful pregnancy or full- and pre-term birth infants after adjustment for disease activity. Similarly, the proportion of overall maternal complications and flares in patients with hypertension in the modified clinical remission or modified LLDAS subgroups also was slightly, but not statistically, higher than in their counterparts, who did not have hypertension. However, the presence of hypertension was significantly associated with overall maternal complications and flares after adjustment for disease activity.

Pregnancy outcomes according to period of pregnancy

As the study covered over 24 years, pregnancy outcomes according to the period of pregnancy were determined (Table 5). Overall, there was no statistically significant difference in fetal or maternal outcomes between the modified clinical remission and modified LLDAS groups, as well as between those groups and their counterparts. However, there was a tendency toward a higher proportion of successful pregnancies, lesser proportion of fetal losses, and fewer maternal complications or flares across all of the subgroups.

DISCUSSION

In the present study, we found that the pregnancy outcomes between SLE patients who attained modified clinical remission and those with modified LLDAS at the time of conception were similar, and agreement in the pregnancy outcomes between these two groups was very high. Although pregnancy outcomes did not reach statistical significance, they were more favorable among patients who achieved modified clinical remission or modified LLDAS than their counterparts. The presence of hypertension was not associated with poor fetal outcomes, but with maternal complications and flares.

Our previous reports also found that active disease at pregnancy, renal involvement ever, and use of prednisolone at >10 mg/day were associated with poor pregnancy outcomes.[23] Other studies showed that active disease prior to or during pregnancy,[8,14,16,24-27] and flares during pregnancy[14,25,28] are clearly associated with adverse pregnancy outcomes in SLE patients. Other factors which are associated with poor pregnancy outcomes include renal involvement during pregnancy,[14,16,25-32] cytopenia,[14,16,26,28,31] serositis,[31] arthritis,[16] hypo-complementem ia,[14,26,28,29,33] and anti-dsDNA antibodies.[16,26,29] These poor prognostic factors are among the variables included in the SLEDAI and cSLEDAI instrument;[19,22] therefore, their absence would exclude the possibility of active disease, and meet remission according to the DORIS definition.[9,10] In this study, we found that pregnancy outcomes among pregnant SLE patients, who achieved modified clinical remission and modified LLDAS, were almost identical to and more favorable than those in their counterparts, although only some of them (e.g., fetal birth weight and the proportion of full-term birth infants) showed a statistically significant difference. These observations supported previous findings that pregnant SLE patients who achieved clinical remission or low disease activity (determined by either the SLEDAI, PGA or SLE pregnancy disease activity index [SLEPDAI] score)[8,14,16,24,26] had better pregnancy outcomes than those who did not. They also supported recent studies showing that pregnant SLE patients who achieved LLDAS at conception had significantly

better maternal and fetal outcomes than those who did not.[15,16,33]

The presence of hypertension[14,25,26,34,35] and anti-phospholipid antibodies (including ACL, LAC, and anti-β2GP1)[14,26-29,34] are among the non-SLE disease activity factors found to associate with poor pregnancy outcomes. However, this study could not find a significant difference in fetal outcomes in the modified clinical remission or modified LLDAS with hypertension subgroups, compared to their counterparts, who did not have hypertension. This is in contrast to many previous reports,[25,26,34,35] which may be due to the small number of patients with hypertension among the subgroups of patients studied. Although the overall maternal complications and flares also showed no statistically significant difference between patients in the modified clinical remission or modified LLDAS with hypertension subgroups, or their counterparts who did not have hypertension, a significant difference was observed only when disease activity was adjusted, thus indicating that hypertension might play a role in adverse maternal complications. The effect of hypertension on adverse maternal outcomes in this study was similar to that in previous reports.[25,35]

In this study, the significantly higher proportion of renal involvement at the time of conception in the non-modified clinical remission and non-modified LLDAS groups was not unexpected, as it was due to the definition of clinical remission and LLDAS. The presence of active renal involvement during pregnancy was associated with poor pregnancy outcomes, which also were reported by the groups in this study,[23] and similarly in many previous reports.[25,26,31] It is interesting that a report from Canada found that active lupus nephritis in pregnancy was not associated with worsened pregnancy outcomes, but was with pregnancy-induced hypertension and flares.[30]

The advance in maternal-fetal medicine and SLE management, including preparation of patients prior to conception, monitoring disease activity and initiation of treatment once a flare occurs, has led to the improvement in pregnancy outcomes in SLE patients.[26,36] This finding was observed also in the authors' previous report.[23] Although this study could not find significantly favorable pregnancy outcomes among the modified clinical remission and modified LLDAS groups, compared to their counterparts, there was a trend of more favorable outcomes in all subgroups in the latest period of pregnancy. Over the last decade, calcineurin inhibitors, particularly cyclosporine and tacrolimus, have been used with precaution during pregnancy, which has led to improved disease control, particularly in patients with active nephritis, resulting in better pregnancy outcomes.[37-39] In addition, a recent study has found that low-dose cyclophosphamide does not affect ovarian function and would be helpful in managing active lupus patients, particularly lupus nephritis patients who desire to be pregnant.[40] It also was found that a longer time interval between the last cyclophosphamide infusion and subsequent pregnancy was associated with favorable pregnancy outcomes.[41]

There were several limitations in this study. The number of pregnant patients was rather small, which might have affected statistical analysis. However, this number was comparable to many previous studies on pregnancy in SLE patients. On the other hand, a retrospective calculation from this study obtained a statistical power of 82%, which is generally acceptable. The use of modified score by excluding PGA in the DORIS and LLDAS definitions and in the SFI, as well as using the cSLEDAI score in LLDAS instruments, made the modified clinical remission and modified LLDAS groups in this study non-compliant with original ones.[9,10,12,21] Therefore, the results from this study might not be compared directly with previous studies that used original instruments.[15,16] Exclusion of PGA from the DORIS definition of remission and LLDAS has never been validated. The PGA is mainly evaluated subjectively and depends on the physician's experience and other factors that may affect their judgment. Studies have shown a very good correlation between PGA and SLEDAI,[42-44] but it can be argued that PGA can capture certain SLE disease activities which the SLEDAI instrument cannot; e.g., gastrointestinal involvement or immune hemolysis. According to the DORIS definition, patients who are in clinical remission (with or without treatment) must have a cSLEDAI score=0, PGA <0.5, prednisolone at ≤5 mg/day, and receive immunosuppressive drugs in addition to hydroxychloroquine (HCQ).[9,10] Thus, if patients have active disease in any

organ manifestations, including gastrointestinal involvement or immune hemolysis that is not captured by the SLEDAI score, they should receive prednisolone at >5 mg/day or have a PGA score of ≥0.5, which precludes them from clinical remission. Similarly, LLDAS attainment allows patients to have a SLEDAI score of ≤4, PGA of ≤1.0, prednisolone at ≤7.5 mg/day, acceptable standard dose of immunosuppressive drugs or biological therapy in addition to HCQ, and no new features of SLE disease activity or any major organ involvement.[12] Thus, if patients develop new severe clinical SLE disease activity or major organ involvement, they also should receive prednisolone at >7.5 mg/day or immunosuppressive drugs and PGA of ≥1, which also precludes them from LLDAS achievement. Therefore, omitting PGA would not have much effect on the assessment of clinical remission or LLDAS.

Using cSLEDAI (which excludes serology) instead of the original SLEDAI instrument clearly could make the modified LLDAS score lower than it should be. However, a previous study showed a very good correlation between cSLEDAI and the original SLEDAI.[19] Thus, using cSLEDAI instead of the SLEDAI for modified LLDAS in this study should not make much difference in SLE activity assessment when compared to original LLDAS. Similar to PGA, the modified LLDAS in this study has never been validated. Therefore, it may be of interest to determine the correlation between LLDAS that includes and excludes serology. Finally, the effect of anti-phospholipid antibodies on pregnancy outcomes was not determined in this study due to the small number of patients who had a positive test.

Although there were several limitations in this study, it has some strength. Disease activity was determined at -6M and -3M to ensure that all pregnant patients in the modified clinical remission and modified LLDAS groups had clinical remission or low disease activity prior to conception. The use of modified clinical remission and modified LLDAS in this study reflects a real-world setting, where serology testing is not routinely available, and PGA is not captured routinely in many centers. In addition, although this study was performed in a single center, all of the SLE patients were treated by a single rheumatology team with a vast experience in the same direction of SLE care and management of pregnant SLE patients, which could be another strength of this study.

In conclusion, pregnancy outcomes in SLE patients who achieved modified clinical remission and modified LLDAS were comparable, and agreement in pregnancy outcomes between these two disease activity statuses was very high. Unfortunately, the use of the modified definition of clinical remission and LLDAS in this study, which has not been validated yet, made it impossible to compare the results directly with studies that used original definitions. Therefore, further studies are needed to confirm these findings.

Acknowledgements: We thank Mrs. Waraporn Sukitawut, Ms. Saowanee Pantana, and Ms. Phimwalan Konkaeo for their secretarial assistance.

Ethics Committee Approval: The study protocol was approved by Chiang Mai University, Faculty of Medicine, Ethics Committee (No. 215/2017). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study design, collect the data, statistical analysis, interpretation the results, wrote manuscript: W.L.; Study design, collect the data, interpretation the results, wrote manuscript: T.T.; Study design, interpretation the results, wrote manuscript: N.K.; Statistical analysis, interpretation the results: A.W.;

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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