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Does cutaneous lupus erythematosus have more favorable pregnancy outcomes than systemic disease? A two-center study

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Key words
Anti-phospholipid antibodies, cutaneous lupus erythematous, pregnancy, pregnancy complications, pregnancy outcome, systemic lupus erythematous

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Objective. To compare pregnancy outcomes in cutaneous lupus erythematosus (CLE) with systemic lupus erythematosus (SLE) and healthy pregnant women. *Design.* Cohort comparative study. *Setting.* Two university maternity centers in Saudi Arabia and Egypt. *Population.* Pregnant women with CLE and SLE and healthy pregnant women. *Methods.* Over a three-year period, 201 participants were allocated to three groups: group 1 (n = 67) contained women with CLE, group 2 (n = 67) women with SLE, and group 3 healthy controls (n = 67). Diagnosis of lupus erythematosus was based on American College of Rheumatology criteria. All participants were followed until delivery. Lupus exacerbation was evaluated by Lupus Activity Index score. ANOVA and chi-squared tests were used to compare obstetrical and neonatal outcomes, and regression analysis was used to define independent factors of adverse pregnancy outcomes. *Main outcome measures.* Pregnancy losses, preterm labor, intrauterine growth restriction, preeclampsia, neonatal intensive care unit admissions, cesarean sections and lupus exacerbations. *Results.* There was no significant difference between groups 1 and 3 in rates of pregnancy loss, preterm labor, preeclampsia, intrauterine growth restriction and neonatal intensive care admission. Group 1 had lower pregnancy loss (p = 0.005), growth restriction (p = 0.001), preeclampsia (p = 0.05), neonatal intensive care admissions (p = 0.001), cesarean section (p = 0.03), lupus exacerbations (p = 0.05) and anti-phospholipid antibodies (p = 0.02) compared with group 2. In groups 1 and 2, lupus exacerbation and anti-phospholipid antibodies were significant independent factors for adverse outcomes. *Conclusions.* Cutaneous lupus erythematosus means comparable pregnancy outcomes to those of the healthy population. Lower rates of disease exacerbation and anti-phospholipid antibodies are potential factors for better pregnancy outcome in CLE compared with SLE.

Abbreviations: aCL-IgG, anti-cardiolipin-IgG; aCL-IgM, anti-cardiolipin-IgM; aPLs, antiphospholipid antibodies; APS, antiphospholipid syndrome; CLE, cutaneous lupus erythematosus; GPL/MPL, immunoglobulin G or M phospholipid; IUGR, intrauterine growth restriction; LAC, lupus anticoagulant; LA, lupus anti-coagulant screening reagent; LE, lupus erythematosus; PE, preeclampsia; SLE, systemic lupus erythematosus; TNF-α, tumor necrosis factor.

Key Message

Cutaneous lupus erythematosus has comparable pregnancy outcomes to those seen in healthy women. Lower rates of disease exacerbation and anti-phospholipid antibodies are conducive to a better pregnancy outcome in cutaneous lupus compared with organ-affecting systemic disease.

Introduction

Systemic lupus erythematosus (SLE) is a systemic medical disorder that has well known adverse maternal and obstetrical outcomes compared with a what is seen among healthy women (1–6). These adverse outcomes

include higher risks of pregnancy loss, preterm labor, pre-eclampsia (PE), intrauterine growth restriction (IUGR) and disease flaring (2–5). Multiple factors are implicated in these adverse outcomes, which include activity at time of conception, disease exacerbation (7), renal involvement (8), increased antiphospholipid antibodies (aPLs) and human tumor necrosis factor-α (TNF-α) (9,10). It is now thought that patients with lupus erythematosus (LE) can be divided into more homogeneous subsets with different pathogenic, histological, therapeutic and prognostic significance (11). In his report, Wallace classified patients with LE to either organ-threatening SLE, such as patients with cardiopulmonary, renal, central nervous system complications, and hematological manifestations or non-organ-threatening disease, such as cutaneous LE (CLE) (12). CLE is considered a major clinical presentation of LE seen in 60–80% of patients. It is the primary sign of the disease in 25% of cases (10,11). Nearly 20% of patients may progress to organ-affecting disease within 5 years of diagnosis (12). As patients with CLE may or may not proceed to organ-affecting disease, many will retain these cutaneous manifestations as the only clinical signs of the disease for long periods during their reproductive age (12). It has previously been reported that CLE patients may have a mild disease course and activity as assessed by LE activity index scores with a possibly lesser form of serological and inflammatory activation (13).

There are insufficient data on clinical obstetrical and neonatal outcomes in women with CLE. We hypothesized that CLE might be associated with more favorable pregnancy outcomes than organ-affecting SLE, as well as compared with healthy pregnant women.

Material and methods

This is a cohort comparative study conducted in cooperation with the Departments of Obstetrics & Gynecology, Rheumatology, Dermatology, Microbiology and Immunology and Physiology in Qassim University, Saudi-Arabia, and Assiut University, Egypt. Pregnant women complaining of LE who attended antenatal, rheumatology and dermatology clinics in maternity-children's hospitals in the Qassim Region and Assiut university hospitals were invited to participate in this study between January 2009 and October 2012. The study design was approved by the Deanship of Scientific Research in Qassim University and the Research Ethical committee in Assiut University. An informed consent for study design, procedures and follow-up was obtained from all participants.

The diagnosis of LE was based on American College of Rheumatology criteria (14). The study included three groups of pregnant participants. *Group 1* included CLE women whose diagnosis was based clinically on cutaneous manifestations only. These manifestations include one or more of the following: (i) malar rash (fixed erythema over the malar eminences), (ii) discoid rash (erythematous raised patches with adherent keratotic scaling, (iii) photosensitivity leading to skin rash over the photo-localizing areas such as the face, V-regions of the chest and extensors of the extremities and hands, and (iv) oral or nasopharyngeal ulceration.

Group 2 included women with organ-threatening SLE whose clinical presentation showed involvement of one or more of other body tissues/organs in the course of the disease regardless of cutaneous manifestations. These systemic non-cutaneous manifestations included: (i) renal disease diagnosed as persistent proteinuria >0.5 g/day or >3+ urine dipstick or cellular casts; (ii) serositis as pleuritis (diagnosed by pleuritic pain, rub or evidence of effusion) or pericarditis (documented by electrocardiogram, rub or evidence of effusion); (iii) CNS manifestations such as seizures or psychosis in the absence of offending drugs or known metabolic derangements; (iv) non-erosive arthritis including two or more peripheral joints, characterized by tenderness, swelling or effusion; and (v) hematological manifestations such as hemolysis, leukopenia (<4000/mm^3 on ≥2 occasions) or thrombocytopenia (<100 000/mm^3). Groups 1 and 2 also had to have one or more of the following serological findings at any time during course of the disease to meet the minimum four criteria to establish an LE diagnosis: (i) positive antinuclear antibody, (ii) anti-double strand-DNA in an abnormal titer, (iii) anti-Smith antibody, and (iv) positive aPLs (15) or lupus anticoagulant (LAC) (14).

Group 3 had age-matched healthy pregnant women as controls who had comparable gestational age at time of recruitment and had no history of repeated abortions or adverse obstetrical outcome.

The sample size was calculated based on previous studies (2,16,17) showing a pregnancy loss rate of 25–83% in SLE patients compared with healthy women without a previous history of repeated abortions, where the pregnancy loss ranges between 12 and 19% (18). As we found no previous studies addressing pregnancy outcome in a selected CLE population, we assumed that those patients might have 20% lower risk of pregnancy loss than SLE. This lower risk could have clinical significance as it approached the range of a healthy population. To demonstrate the statistical assumed difference between the three groups setting α at 0.05 and β at 0.2, we enrolled a total of 201 participants who were allocated into groups in a ratio of 1:1:1.

All participants including controls were aged between 18 and 40 years to avoid an effect of age extremes on obstetrical outcomes. Also, we included women early in the first trimester just after establishment of an intrauter-

ine gestational sac to catch early pregnancy complications. At baseline, a full history was taken, including obstetric antecedents, LE duration, previous and current disease manifestations and therapy. Baseline investigations (which were then repeated on a monthly basis) included blood count, serum creatinine, proteins, glucose, uric acid, urinalysis, 24-h urine protein and a full immunological profile. This included determination of antinuclear antibody, anti-double strand-DNA, anti-Smith antibody (QUANTA-Lite™ ELISA; INOVA Diagnostics Inc., San Diego, CA, USA) and human TNF-α (Human TNF-α ELISA Set; Sino Biological Inc., Beijing, China). Anticardiolipin IgG/IgM (aCL) was measured with an ELISA kit (REAADS® Anti-Cardiolipin IgG/IgM Semi-Quantitative Test Kit; Corgenix Inc., Broomfield, CO, USA). According to the revised international consensus for antiphospholipid syndrome (APS) (19), the cut-off level of aCL titer used for diagnosis of APS was >40 GPL/MPL (immunoglobulin G or M phospholipid) on two occasions 12 weeks apart in addition to at least one clinical criterion. Those with an aCL titer less than this value but more than 20 GPL/MPL with no associated clinical criteria were considered positive for aCL only. Those without aCL or titers <20 GPL/MPL were counted as normal. In healthy controls, aCL was also measured to identify and exclude women with asymptomatic antibodies who might have had a medium to high titer (>20 GPL/MPL). LAC was measured with the Dade Behring Sysmex system (Siemens AG, Erlangen, Germany). This system is a fully automated coagulation analyzer that detects LAC using a lupus anti-coagulant (LA) 1 screening reagent/LA2 confirmation test kit. The LA 1 screening reagent contains Russell's viper venom which initiates plasma clotting by activation of factor X, so the presence of LA antibodies prolongs the LA1 screening reagent clotting time. LA2 confirmation is a similar to LA1 screening but contains a high phospholipid concentration, which counteracts the LA antibody and corrects the clotting time. The test was considered positive if the LA1/LA2 ratio was >1.2 as determined by the values obtained from healthy controls.

Pregnancy was followed every 4 weeks until the 28th week and then twice monthly up to 32 weeks and thereafter weekly until delivery. Ultrasound examination was performed in the first trimester to confirm gestational age and then every 1–2 weeks in the third trimester for evaluation of fetal activity and/or growth. From 34 weeks onwards, cardiotocography was obtained on a weekly basis. Doppler velocimetry of uterine and umbilical arteries was arranged in women with suspected IUGR. According to previous studies, women with an obstetrical history of APS (4) or those with positive aPLs only (1) received low dose aspirin (75 mg/day) and low molecular weight heparin (enoxaparin) 40 mg/0.4/day subcutaneously (Lovenox®; Sanofi-Aventis, Bridgewater, NJ, USA) once pregnancy was established and until term. The patients continued to take their prescribed preconception LE medications during pregnancy, including prednisone, which was also prescribed to control disease activity. Contraindicated drugs during pregnancy, such as methotrexate or cyclosporin, were stopped. Disease exacerbation was recorded with the Lupus Activity Index in Pregnancy (20). Exacerbation was defined as an increase ≥0.25 in the activity index compared with the previous visit evaluation.

A miscarriage was defined as pregnancy loss before 24 weeks and preterm delivery as delivery before 37th week. Diagnosis of IUGR was based on population-based growth curves with estimated fetal weight <10th percentile associated with abnormal high Doppler indices (21). The primary measured outcome was pregnancy loss, which included miscarriages and intrauterine fetal death. The secondary outcomes were preterm labor, PE, cesarean section rate, disease flaring, admission to neonatal care unit (NCU) and neonatal mortality.

Data were analyzed using SPSS and PRISM statistical packages and expressed as mean ± SD and/or percentages. Unpaired *t*-tests and/or one-way ANOVA were used for mean comparisons, and chi-squared or Fisher's exact test with calculation of odds ratio (OR) and 95% confidence intervals (CI) were used to compare categorical variables. Univariate and multivariate logistic regression analysis was done to predict adverse pregnancy outcomes in both LE groups. A p-value ≤0.05 was considered significant.

Results

In total, 201 participants were recruited from both centers and allocated into group 1 ($n = 67$), group 2 ($n = 67$) and group 3 (controls, $n = 67$). At Qassim center, 37 women (55%) were recruited in group 1, 33 (49%) in group 2 and 34 (50%) in group 3, while the other women were allocated from the Assiut center. Table 1 demonstrates that all groups had comparable parity, maternal and gestational age at time of recruitment. There was a significantly higher number of women with a history of miscarriage in group 2 than in groups 1 and 3.

Table 2 shows that there was no significant difference between groups 1 and 2 in disease duration, disease activity within 6 months before pregnancy, cutaneous manifestations, TNF-α or preconception medications. However, disease flaring during the current pregnancy and positive aCL-IgM/IgG and LAC were significantly higher in group 2. The total number of patients with one or more positive aPLs was 13/67 (19%) in group 1 vs. 33/67 (49%) in group 2. All were treated by low dose aspirin and heparin. Two women (3%) in group 1 and

Table 1. Baseline clinical characteristics of participants in all study groups.

Clinical characteristic	Group (1) (CLE), $n = 67$	Group (2) (SLE), $n = 67$	Group (3) (Control), $n = 67$	p-value	OR (95% CI)
Age (years), mean ± SD (range)	24.72 ± 3.81 (19–38)	25.83 ± 3.98 (18–39)	25.51 ± 3.40 (19–37)	0.211*	–
Previous deliveries, mean ± SD (range)	2.32 ± 1.01 (0–4)	2.51 ± 1.33 (0–3)	2.57 ± 1.28 (0–5)	0.462*	–
Previous abortions, mean ± SD (range)	0.96 ± 1.01 (0–3)	1.61 ± 1.05 (0–4)	0.81 ± 0.72 (0–2)	<0.001 (1) vs. (2)* >0.05 (1) vs. (3)* <0.001 (2) vs. (3)*	–
Previous PTD, no. (%)	11 (16.4)	15 (22.3)	4 (5.9)	0.5 (1) vs. (2)† 0.1 (3) vs. (1)† 0.01 (3) vs. (2)†	0.68 (0.28–1.61) 0.32 (0.09–1.07) 0.22 (0.06–0.70)
Previous stillbirth, no. (%)	6 (9.0)	11 (16.4)	4 (5.9)	0.3 (1) vs. (2)† 0.7 (3) vs. (1)† 0.1 (3) vs. (2)†	0.50 (0.17–1.44) 0.64 (0.17–2.40) 0.32 (0.09–1.07)
G A (weeks), mean ± SD (range)	8.00 ± 2.09 (5–13)	8.54 ± 2.32 (5–13)	7.85 ± 2.13 (5–13)	0.159*	–

CI, confidence interval; CLE, cutaneous lupus erythematosus; GA, gestational age at recruitment; OR, odds ratio; PTD, preterm delivery; SLE, systemic lupus erythematosus.
*One-way ANOVA and Tukey post hoc test for comparison of means (PRISM statistical package).
†Fisher's exact test for comparison of percentages (SPSS statistical package).

Table 2. Clinical and laboratory findings of lupus disease in current pregnancy in cutaneous and systemic lupus erythematosus patients.

Clinical characteristic	Group (1) (CLE), $n = 67$		Group (2) (SLE), $n = 67$		OR (95% CI)	p-value
Duration of the disease (years), mean ± SD (range)	4.87 ± 3.05 (1–11)		5.84 ± 3.32 (1–12)		–	0.08*
	n	%	n	%		
Active disease ≤6 months before current pregnancy	2	3.0	4	6.0	0.78 (0.21–5.98)	0.5†
Flaring in current pregnancy	11	16.4	30	44.8	0.23 (0.07–0.76)	0.02†
Cutaneous lesions	54	80.6	48	71.6	1.70 (0.52–5.55)	0.5†
Photosensitivity	63	94.0	52	77.6	4.22 (0.80–22.28)	0.1†
ANA	54	80.6	65	97.0	0.13 (0.01–1.23)	0.1†
Anti dsDNA	48	71.6	61	71.0	0.26 (0.06–1.08)	0.1†
Anti phospholipids	11	16.4	30	44.8	0.23 (0.07–0.76)	0.02†
aCL IgM	11	16.4	33	49.0	0.20 (0.06–0.67)	0.01†
aCL IgG	13	19.4	32	47.8	0.25 (0.08–0.79)	0.03†
LAC						
Anti-Smith antibody	27	40.2	30	45.0	0.76 (0.27–2.10)	0.7†
Human TNF-α	26	38.8	37	55.2	0.52 (0.18–1.43)	0.3†
Treatment						
No treatment	14	20.8	8	11.9	–	0.4‡
NSAI	8	11.9	13	19.6		
Steroids	26	38.6	21	31.3		
Hydroxychloroquine	13	19.4	11	16.4		
Azathioprine	0	0.0	2	2.9		
Combinations	6	8.9	12	17.9		

aCL, anticardiolipin antibody; ANA, anti nuclear antibody; CI, confidence interval; CLE, cutaneous lupus erythematosus; LAC, lupus anticoagulant; NSAI, non-steroidal anti-inflammatory; OR, odds ratio; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.
*Unpaired t-test.
†Fisher's exact test.
‡Chi-squared test.

15 (22%) in group 2 had full obstetrical APS based on obstetrical history plus one or more positive laboratory tests. The remaining patients with positive aPLs in both groups had neither sufficient obstetrical criteria nor a history of thrombosis for establishment of APS diagnosis (data not shown in Table 2).

Table 3. Maternal and pregnancy outcomes in all groups of the study.

Pregnancy outcome	Group (1) (CLE), (n = 67)	Group (2) (SLE), (n = 67)	Group (3) (control), (n = 67)	p-value*†	OR (95% CI)
GA at delivery (W), mean ± SD (range)	37.69 ± 2.92 (28–39)	35.78 ± 3.51 (28–38)	37.87 ± 2.19 (28–41)	(1) vs. (2) <0.001 (1) vs. (3) 0.8 (3) vs. (2) <0.001	–

	n	%	n	%	n	%		
Pregnancy loss	9	13.4	24	35.8	6	8.9	(1) vs. (2) 0.005	0.27 (0.11–0.65)
							(3) vs. (1) 0.6	0.63 (0.21–1.89)
							(3) vs. (2) 0.000	0.17 (0.06–0.47)
Preterm delivery	11	16.4	17	25.3	4	5.9	(2) vs. (1) 0.3	1.73 (0.74–4.0)
							(1) vs. (3) 0.1	3.0 (0.93–10.2)
							(2) vs. (3) 0.004	5.35 (1.69–16.9)
IUGR	6	9.0	22	32.8	2	2.9	(1) vs. (2) 0.001	0.20 (0.07–0.53)
							(3) vs. (1) 0.2	0.31 (0.06–1.6)
							(3) vs. (2) 0.000	0.06 (0.01–0.28)
PE/superimposed/eclampsia	7	10.4	17	25.4	4	5.8	(1) vs. (2) 0.05	0.34 (0.13–0.89)
							(3) vs. (1) 0.5	0.54 (0.15–1.95)
							(3) vs. (2) 0.004	0.18 (0.05–0.59)
CS delivery	11	16.4	24	35.8	10	14.9	(2) vs. (1) 0.03	2.84 (1.25–6.43)
							(1) vs. (3) 1.0	1.11 (0.44–2.84)
							(2) vs. (3) 0.009	3.18 (1.37–7.34)
NICU admission	6	9.0	22	32.8	4	5.9	(1) vs. (2) 0.001	0.22 (0.07–0.53)
							(3) vs. (1) 0.6	0.64 (0.17–2.4)
							(3) vs. (2) 0.000	0.13 (0.04–0.40)
Neonatal death	2	2.9	6	9.0	0	0.0	(1) vs. (2) 0.6	0.31 (0.03–3.16)

CI, confidence interval; CLE, cutaneous lupus erythematosus; CS, cesarean section; GA, gestational age; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; OR, odds ratio; PE, preeclampsia; SLE, systemic lupus erythematosus.
*One-way ANOVA test with Tukey post hoc test to compare means (PRISM statistical package).
†Fisher's exact test to compare percentages (SPSS statistical package).

As shown in Table 3, group 1 had a significantly higher gestational age at delivery and lower pregnancy losses (p = 0.005), as well as IUGR, PE, cesarean section and NICU admission rates in comparison with group 2. Compared with controls, group 1 had comparable obstetrical and neonatal outcomes. As seen in Table 3, group 2 had a significantly lower mean gestational age at delivery and higher pregnancy losses (p = 0.000), and preterm labor, PE, IUGR, cesarean section and NICU admission rates compared with group 3.

Table 4. Comparison of obstetrical outcomes in both lupus groups in relation to antiphospholipid antibody (aPLs) status.

	Women with positive aPLs						Women with negative aPLs					
	CLE, (n = 13)		SLE, (n = 33)				CLE, (n = 54)		SLE, (n = 34)			
Outcome	n	%	n	%	p-Value	OR (95% CI)	n	%	n	%	p-value	OR (95% CI)
Pregnancy loss	7	53.8	18	54.5	1.0	0.97 (0.26–3.5)	2	3.7	6	17.6	0.05	0.17 (0.03–0.94)
Preterm delivery	4	30.8	10	30.3	1.0	0.97 (0.24–3.93)	7	13.0	7	20.6	0.3	1.7 (0.55–5.49)
IUGR	3	23.1	10	33.3	0.7	0.69 (0.15–3.05)	3	5.3	12	35.3	0.001	0.10 (0.02–0.42)
PE/superimposed/eclampsia	2	15.4	10	33.3	0.4	0.41 (0.07–2.24)	5	9.3	7	20.6	0.2	0.39 (0.11–1.36)
CS	3	23.1	17	51.5	0.1	3.54 (0.82–15.2)	8	14.8	7	20.6	0.5	1.49 (0.48–4.57)
NICU admission	4	30.8	14	42.4	0.5	0.6 (0.15–2.36)	2	3.7	8	23.5	0.01	0.12 (0.02–0.63)
Neonatal death	2	15.4	4	12.1	1.0	1.31 (0.21–8.24)	0	0	2	5.9	0.1	–

CI, confidence interval; CLE, cutaneous lupus erythematosus; CS, cesarean section; IUGR, intrauterine growth restriction; NICU, neonatal care unit; OR, odds ratio; PE, preeclampsia; SLE, systemic lupus erythematosus.

Table 5. Prediction of adverse pregnancy outcomes in CLE and SLE patients by univariate logistic regression analysis.

	Group (1) CLE, (n = 67)		Group (2) SLE, (n = 67)	
Clinical/lab parameter	Pregnancy loss p-value Exp B (95% CI)	IUGR p-value Exp B (95% CI)	Pregnancy loss p-value Exp B (95% CI)	IUGR p-value Exp B (95% CI)
Age*	0.8 0.97 (0.76–1.24)	0.6 0.89 (0.60–1.33)	0.1 1. 24 (0.95–1.61)	0.8 0.97 (0.72–1.32)
Parity†	0.5 0.73 (0.27–1.93)	0.9 0.97 (0.38–2.48)	0.8 1. 07 (0.60–1.89)	0.4 0.73 (0.36–1.48)
Previous abortion*	0.1 1.98 (0.84–4.65)	0.8 0.86 (0.27–2.78)	0.7 1. 12 (0.54–2.32)	0.5 0.77 (0.32–1.86)
Disease duration *	0.01 1.78 (1.12–2.81)	0.02 1.77 (1.08–2.90)	0.02 1.40 (1.04–1.88)	0.05 1.46 (1.00–2.14)
Flaring in current pregnancy*	0.007 37.9 (2.73–27.97)	0.2 5.33 (0.25–110.76)	0.004 28.78 (2.89–286.11)	0.01 1.68 (1.11–2.91)
aCL IgM*	0.04 9.00 (1.03–78.57)	0.05 16.0 (0.95–267.03)	0.05 22.49 (2.31–218.18)	0.4 2.25 (0.34–14.69)
aCL IgG*	0.04 0.11 (0.01–0.97)	0.05 16.0 (0.95–267.03)	0.004 28.78 (2.89–286.11)	0.5 1.65 (0.26–10.31)
LAC*	0.09 5.66 (0.75–42.58)	0.5 2.5 (0.16–37.25)	0.007 22.49 (2.31–218.18)	0.8 0.88 (0.12–6.19)
Renal manifestation*	–	–	0.01 10.0 (1.62–61.46)	0.1 4.00 (0.61–26.12)

aCL, anticardiolipin antibody; CI, confidence interval; CLE, cutaneous lupus erythematosus; IUGR, intrauterine growth restriction; LAC, lupus anticoagulant; SLE, systemic lupus erythematosus; TNF-α, tumor necrosis factor.

*Parameters had positive correlation (positive β value) with adverse pregnancy outcomes.

†Parameters had negative correlation (negative β value) with adverse pregnancy outcomes.

Table 4 shows the comparison of obstetrical outcomes in groups 1 and 2 in relation to aPL antibody status. There was no significant difference in obstetrical and neonatal outcomes between subgroups who were positive for aPLs. Those with a negative aPLs profile showed significantly higher rates of pregnancy loss, IUGR and NICU admissions in group 2 than in group 1.

Univariate logistic regression analysis in group 2 (Table 5), demonstrated that longer disease duration and disease flaring were associated with significantly higher pregnancy loss and IUGR rates. In group 2, aCL-IgM/IgG, LAC and lupus nephritis were associated with a significantly higher pregnancy loss. In group 1, longer disease duration and aPLs were associated with significantly higher pregnancy losses and IUGR rates, while disease flaring predicted more pregnancy loss.

In an additional regression model (data not shown) these clinical and laboratory parameters were tested in one step within each group by multivariate analysis to predict any of these adverse outcomes. In group 1, pregnancy loss and IUGR outcomes were still significantly predicted by disease flaring (OR 2.64, 95% CI 1.17–7.56, $p = 0.02$), whereas in group 2 this was predicted by lupus flaring (OR 2.54, 95% CI 1.05–6.14, $p = 0.05$) and aCL-IgG (OR 4.54, 95% CI 1.13–8.14, $p = 0.04$).

Discussion

The current study demonstrated that women with CLE, compared with those with SLE, had significantly lower rates of adverse outcomes and higher gestational age at delivery. When compared with controls, CLE patients had comparable obstetrical outcomes, whereas SLE was associated with significantly higher adverse outcomes. This demonstrates clearly that women with CLE lie adjacent to the normal rate of an imaginary scale of adverse pregnancy outcomes in LE. This difference could not be explained on the basis of heterogeneity in the study population as both centers were represented almost equally in all groups.

The rates of pregnancy loss in women with SLE and CLE (35.8 and 13.4%) are in agreement with the reported 4–43% (mean 19.5 ± 1.6) in a review of 45 studies including unselected LE populations (2). Those authors also reported a pregnancy loss mean of 18.3 in their case-control study that included 108 SLE women (2). Comparison of pregnancy outcomes before and after diagnosis of SLE, suggests that such loss was more prevalent after than before diagnosis of SLE (22). The lower loss rates seen in the current CLE women could be attributed to multiple factors. The first is the lower rate of disease flaring in this

group compared with the rate in SLE (16 vs. 45%), as has been well documented (22–26). A loss rate of 25–52% among patients with active SLE compared to 8–12% in quiescent disease has been reported, especially at the onset of pregnancy (2). Overall, the rate of lupus flaring in pregnancy ranges from 20 to 50% (2,22–26) as seen in the current study. The different definitions of lupus flare probably contribute to these wide ranges but were minimized in the current study by the use of specific clinical guidelines (4) and the Lupus Activity Index in Pregnancy scoring system (20) to determine accurately the diagnosis of flaring and to differentiate it from other pregnancy-related complications. There was no significant difference between either LE groups in terms of the levels of TNF-α and consequently this parameter could not be used as an indicator of disease activity during pregnancy.

We found lower aPLs and LAC in women with CLE than in those with SLE (19 vs. 48%), which importantly could be a second factor explaining the higher pregnancy loss in the SLE group. Previous studies (2,16,23,27,28) have reported that 10–60% of SLE patients have aPLs and/or LAC. The association between these antibodies and pregnancy loss, IUGR and PE has been documented (16,17,23). Lack of sound implantation and development of placental vasculature thrombosis are possible mechanisms (2,17). The presence of these antibodies is associated with pregnancy loss as high as 30–83%, compared with 4–43% in aPLs negative women (2). Fetal outcome was shown to be significantly improved by treatment with heparin and low dose aspirin in those women (1,2). This therapeutic intervention was used in the current material and was expected to improve pregnancy survival and other outcomes more in the SLE than the CLE group, due to the higher prevalence of aPLs and LAC. The third possible factor for higher pregnancy loss seen in SLE is the presence of lupus nephritis, a factor completely absent in the CLE group. We noted renal manifestations in nearly 45% of the SLE group; active renal disease has been reported to be associated with 8–24% of pregnancy loss and neonatal deaths (2,17,25,28). However, with inactive nephritis, the pregnancy outcome is usually favorable (28).

Although gestational age at delivery was significantly higher in the CLE than the SLE group, the difference in preterm birth rate was not significant. Analysis of 43 studies in a review article (2) has shown a 4–62% preterm delivery rate among SLE patients compared with 4–9% in the general population. This wide range might be due to different definitions and causes of prematurity in SLE. Higher exacerbation rates and positive aPLs are possible explanations for the higher number of preterm deliveries seen in the current SLE women (3,6,16,22–24). Other reasons for preterm delivery include development of maternal hypertension (6,24,25), PE (28) and increased prevalence of preterm pre-labor rupture of membranes (29,30). In addition, it has been reported that steroid treatment during pregnancy, especially with doses >15 mg/day, may be associated with increased risk of preterm delivery, as it may impair placental function and induce premature rupture of membranes (2,31). In this study, both of the LE groups received extra doses of steroids to control exacerbations during pregnancy. This could be another factor masking the difference in the rate of preterm delivery between LE groups.

We reported a 9% IUGR rate in women with CLE compared with 32% in those with SLE. The latter is not in line with a reported range of 10–20% in SLE patients (2,6,22–25,28). High rates of flaring, PE and aPLs (23,24,28,30) could be possible explanations. In addition, most of these studies evaluated IUGR in unselected LE populations, which may explain the lower rates.

Subgroup analysis by antiphospholipid status did not show significant differences in obstetrical and neonatal outcomes between LE groups if the women had APS or were positive for aPLs. The situation was different for those with negative aPLs, who showed more prevalent pregnancy losses and IUGR in SLE than CLE women. This reflects the important role of aPLs in generating adverse outcomes regardless of the organs affected during the course of the disease. For those with negative aPLs, renal involvement and exacerbation of the disease in SLE women remained as the predominant risk factors affecting obstetrical and neonatal outcomes (2,7,8,17).

The regression analysis in both LE groups showed that long disease duration, lupus flaring, aPLs and lupus nephritis in SLE were associated with increased risk of adverse obstetrical outcomes. Even after accounting for clinical and laboratory variables that could affect the outcome in a multivariate regression model, we found disease exacerbation and aPLs present in SLE patients, and exacerbations in CLE were still significant independent factors of adverse outcomes. This reflects the importance of these variables for prognosis and preconception counseling of LE patients. The higher adverse obstetrical outcomes seen in SLE were also reflected in the cesarean section and NICU rates, which were significantly higher in SLE patients. Neonatal mortality was comparable between LE groups but as the total number of deaths was small, we cannot draw conclusions about this vital neonatal outcome.

In conclusion, patients with CLE have more favorable maternal and pregnancy outcomes than seen in women with organ-affecting SLE when both are compared with healthy women. The lower rates of disease flaring and aPLs and absence of lupus nephritis are the potential factors behind this better outcome. Well organized ran-

domized clinical trials are necessary before concluding that patients with CLE are not in need of the extra antenatal work-up done for SLE patients. Until then, all LE patients require careful obstetrical care.

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