Outcome of 69 Pregnancies within a Multinational Population with Systemic Lupus Erythematosus in Qatar

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Abstract: The aim of this study is to determine the frequencies of abnormal pregnancy outcomes in a cohort of patients with systemic lupus erythematosus (SLE). Data of 69 pregnancies of 37 SLE patients were analyzed retrospectively. Lupus activity was assessed based on SLE Disease Activity Index (SLEDAI) criteria. Compared with pregnancies without Lupus nephritis (LN), pregnancies with LN were associated with a higher risk of still birth (p=0.092), higher rate of eclampsia (p=0.103), intrauterine growth restriction (IUGR) (p=0.556), and pregnancy induced hypertension (PIH) (p=0.412). PIH (17.4% vs 11.1%), IUGR (34.7% vs 11.8%), preterm delivery (26.1 % vs 11.8%), still birth (13% Vs 5.6%) and eclampsia (13% Vs 0%), all were observed to be higher in active lupus patients compared to those in remission. However, these differences were not statistically significant (p>0.05). Absence of LN, proteinuria and low complement component 3 (C3) were potential (p<0.15) predictors for live births. Anti-Ro antibodies, high anti-double stranded DNA antibody (anti-dsDNA), and low C3 were strongly associated with pre-term live births and Anti-Ro antibodies was significantly associated with IUGR. In conclusion SLE in pregnancies in a multinational population in Qatar was associated with higher adverse pregnancy outcomes. Disease activity during pregnancy, proteinuria, LN and eclampsia/preeclampsia were all negatively associated with pregnancy outcome such as IUGR, still births and preterm delivery. Laboratory parameters such as presence of Anti Ro/La antibody and low level of C3 were also associated with adverse pregnancy outcome.

Keywords: Systemic lupus erythematosus, pregnancy, outcome, Qatar, Lupus nephritis.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-system autoimmune connective tissue disorder that primarily affects women of childbearing age. Although advances in the treatment of SLE and better obstetric care for the past decades have allowed more women with SLE to achieve successful pregnancies, SLE remains an important contributor to maternal and fetal morbidity and mortality. It is recognized that SLE may increase the incidence of pregnancy complications, including spontaneous abortion, premature delivery, and pre-eclampsia. Patients with SLE are also reported to have higher rates of fetal complications such as preterm delivery and intrauterine growth restriction (IUGR) [1, 2]. In addition, the rate of early pregnancy loss has been reported to be twice that of non-SLE pregnancies, and the rate of preterm delivery to be 17–54% [3-5].

Unfavorable pregnancy outcomes have been reported to be associated with specific factors, including active disease during pregnancy, renal involvement, hypocomplementemia, and antibodies to Ro/SSA, etc. There are few reports on pregnancies in SLE patients from Asia, and especially the Middle East [3, 6, 27]. This study was undertaken to determine and investigate pregnancy outcomes, and the clinical and laboratory factors predicting adverse fetal and maternal outcomes with SLE within a multinational population in Qatar. We have a specialized pregnancy clinic for rheumatic diseases where all patients with SLE are referred, even before conception, when women are planning for pregnancy and also for follow up during pregnancy.

MATERIALS AND METHODS

A retrospective study of 69 pregnancies of 37 SLE patients from January 2005 to July 2012 at Hamad General Hospital in Qatar was analyzed. SLE was diagnosed according to 1997 update of 1982 ACR criteria [7]. SLE disease activities during pregnancy were retrospectively evaluated using the SLE Disease Activity Index (SLEDAI) [8]. Medical charts were reviewed to record demographic and laboratory data, SLE clinical manifestations and treatment, maternal SLE status and pregnancy data. Laboratory data included complete blood count, urinalysis, renal function test, antinuclear antibodies (ANA), anti-dsDNA, anti-Ro/SSA antibodies, anti-La/SSB antibodies, antiphospholipid antibodies (aPL), and C3 and complement component 4 (C4). The pregnancy outcomes were live births including term and preterm

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births, gestational age at birth in weeks, pregnancy loss including miscarriages, stillbirths, and neonatal deaths (NND), infant birth weight, and IUGR. Active SLE was defined as SLEDAI >4, with one of the organs including liver, heart, lung, brain, or hematological system involved. Inactive SLE was defined as SLEDAI ≤4, with none of the organs involved. Active LN was characterized by proteinuria, hematuria, hypocomplementemia, hypertension, and elevated anti-dsDNA [1, 9]. Proteinuria was defined as random urine protein >300 mg/l or 24 h urine protein excretion >0.5 g. Preterm birth was defined as a live birth occurring before 37 weeks of gestation, stillbirths as no signs of life in a fetus delivered after 24 weeks of gestation, and low birth weight as <2.5 kg birth weight of infant at term. Hypertension was considered present if systolic blood pressure was >140 mmHg and/or diastolic blood pressure >90 mmHg in sitting position in three consecutive measurements, or if antihypertensive drugs were used.

Pregnancy outcomes were compared between different clinical and laboratory subsets of SLE including LN, anti-Ro/SSA antibodies, anti-La/SSB antibodies, C3 and C4, aPLs, and anti-dsDNA. Pregnancy outcomes were also compared between active lupus and lupus in remission.

The study was approved by the ethics committee of Hamad Medical Corporation (RC/12185/2012).

Statistical Analysis

A well-structured data capture form in view of research study design and objectives was designed and created to collect all required data. Descriptive statistics were used to summarize demographic, laboratory, radiological and other clinical characteristics of the patients. Q-Q Plot was used to test for normality of the data.

Associations between two or more qualitative or categorical variables were assessed using chi-square ($\chi 2$) test and Fisher Exact test as appropriate, or Yates corrected chi-square. Quantitative data mean between active and remission groups were compared and analyzed using unpaired t test. Relationship between two quantitative variables will be examined using Pearson's and Spearman's correlation coefficients. Univariate and multivariate logistic regression methods were used to assess the predictive values of each predictor or risk factors (such as LN, anti-Ro antibodies, anti-La antibodies, aPLs, anti-ds DNA, proteinuria and C3) for pregnancy outcomes (live births, preterm births and IUGR) and results were presented and reported in odds ratio (OR) and associated 95% CI. All statistical analyses was carried out using statistical packages SPSS 21.0 (SPSS Inc. Chicago, IL) and Epi InfoTM 2000 (Centres for Disease Control and Prevention, Atlanta, GA).

RESULTS

Baseline Demographic, Laboratory and Clinical Characteristics of Pregnant Women

There were 69 pregnancies from 37 SLE patients. Among these, 35 pregnancies were Qatar nationals, 5 each from India and Indonesia, and 4 each from Saudi

Table 1: Baseline Demographic, Laboratory and Clinical Characteristics

Number of pregnancies/number of patients	69/37
Average number of pregnancies after SLE	2.72±1.5
Average number of pregnancies	3.73±1.8
Diagnosed during pregnancy	11(15.9%)
Age at conception (years)	34.5±5.4
Gestational age at delivery (weeks)	37.4±2.8
Active disease during pregnancy	18(26.1%)
past history of APLS with pregnancy loss	3(4.3%)
aPLs, positive	18(26.1%)
Anti-SSA(Ro) antibody	23(33.3%)
Anti-SSB(La) antibody	13(18.8%)
Received cyclophosphamide before pregnancy	5(7.2%)
Glucocorticoid	37(53.6%)
Hydroxychloroquine	45(65.2%)
Azathioprine	21(30.4%)
Cyclosporine	2(2.9%)
Anti-DNA	19(27.5%)
lupus nephritis	7(10.1%)
Pregnancy Induced Hypertension	7(10.1%)
Proteinuria	16(23.1%)
Miscarriage	10(14.5%)
Stillbirth	4(5.8%)
Live birth	54(78.3%)
Preterm	11(15.9%)
IUGR*	14(20.3%)
Eclampsia	4(5.8%)
Preeclampsia	3(4.3%)

*IUGR: Intrauterine Growth Retardation.

Arabia, Egypt and Oman. Other nationalities were Philippine, Iraq, Lebanon, Sudan, UAE and South Africa. Results among different nationalities were not compared. Mean age at the time of conception was 34.5±5.4 years. Mean numbers of pregnancies and pregnancies after SLE onset were 3.73±1.8 and 2.72±1.5, respectively. Mean gestational age at delivery was 37.4±2.85 weeks. Of the 69 women who conceived, abortion occurred in 10 pregnancies and from remaining 59 pregnancies, 18 (30.5%) were in remission, 23 (39%) were in active SLE and the disease status was not known in 18 (30.5%). There were 54 (78.3%) live births, 10 (14.5%) miscarriages, 4 (5.8%) stillbirth, 14 (20.3%) IUGR, 4 (5.8%) eclampsia, and 7 (10.1%) had LN. 18(26.1%) were positive for aPLs and among these, three were secondary Antiphospholipid syndrome. Anti-Ro and anti-La antibodies were positive in 23 (33.3%) and 13 (18.8%) respectively. As a treatment of SLE, 45 (65.2%) received hydroxychloroquine, 37 (53.6%) received glucocorticoid (type and dose was not recorded) and 21 (30.4%) received azathioprine (Table **1**). Interestingly, 5 (7%) patients received cyclophosphamide before pregnancy.

Pregnancy Outcomes in Patients with Disease Status of SLE During Pregnancy

The adverse pregnancy outcomes were higher in active SLE compared to patients in remission, however these differences did not reach to statistical significance (see Table **2**).

Pregnancy Outcomes in Different SLE Subgroups

Pregnancy outcomes (stillbirths, neonatal deaths, live births) were significantly worse in LN (p=0.099) and in patients with low platelet counts (p=0.046) (Table **3**). Compared with pregnancies without LN (n=44), pregnancies with LN (n=7) were associated with a higher risk of still birth (28.6% vs. 4.5%, p=0.092), higher rate of eclampsia (28.6% vs. 4.9%, p=0.103), IUGR (42.9% vs. 24.3%, p=0.556), and PIH (28.6% vs. 9.8%, p=0.412). The percentage of live births were higher in pregnancies without LN compared to patients with LN (42/44, 95.5% vs. 5/7, 71.4%, p=0.092), and live births were significantly higher in pregnancies without eclampsia compared to pregnancies with eclampsia (49/52, 94.2% vs. 2/4, 50%, p=0.037). Similar trends were observed in cases of preeclampsia. Both eclampsia and preeclampsia were associated with a higher rate of still birth.

Still birth and preterm delivery were found to be higher in pregnancies with proteinuria. Among the laboratory parameters, presence of anti-Ro antibody was found to be significantly associated with IUGR (8/18, 44.4% vs. 6/37, 16.2%, p=0.034). Only one case of neonatal heart block was found in which anti Ro/La antibody was positive. Low levels of C3 was associated

Table 2: Pregnancy Outcomes in SLE Patients with Disease Status of SLE During Pregnancy

	Activity during pregnancy		P value
	Remission (n=18)	Active (n=23)	
Gestational age at delivery	37.17±3.35	34.5±5.4	0.789
Birth weight	2.87±0.60	2.68±0.64	0.360
Delivery mode			0.238
Vaginal delivery	12(66.7%)	19(82.6%)	
Cesarean delivery	6(33.3%)	4(17.4%)	
PIH	2(11.8%)	4(17.4%)	0.572
IUGR	2(11.8%)	8(34.7%)	0.081
Preterm birth	2(11.8%)	6(26.1%)	0.153
Live Birth	17(94.4%)	20(87%)	0.423
Stillbirth	1(5.6%)	3(13%)	0.423
Eclampsia	0(0%)	3(13%)	0.111
Pre-eclampsia	1(5.6%)	1(4.3%)	0.859
Neonatal death	1(5.6%)	0(0%)	0.249
Anti-Ro	3(16.7%)	10(43.5%)	0.067
APL	5(27.8%)	4(17.4%)	0.47

Table 3: Comparison of Pregnancy Outcomes According to Different SLE Characteristics

	No. of pregnancies	Pregnancy Outcomes					Delivery			Complications-49 Yes 20 No 29			
	69**	Miscarriage 10(14.5%)	Stillbirths 4(5.8%)	Neonatal deaths 1(1.4%)	Live births 54(78.3%)	p = value*	N	Pre term	p = value*	N †	IUGR	Eclampsia	Pre-Eclampsia	p
Nephritis														
Yes	7		2(28.6)	0(0)	5(71.4)	0.022	5	2(40)	0.372	7	3(42.8)	2(28.6)	0(0)	0.379
No	44		1(2.3)	1(2.3)	42(95.5)		41	9(22)		41	10(24.3)	2(4.88)	2(4.88)	
Anti Ro,														
Yes	23	4(17.4%)	0(0)	1(4.3)	18(78.3)	0.184	17	6(35.3)	0.082	16	7(43.8)	2(12.5)	1(6.25)	0.815
No	43	4(9.3%)	4(9.3)	0(0)	35(81.4)		35	5(14.2)		33	6(18.2)	2(6.06)	2(6.06)	
Anti La														
Yes	13	3(23.1)	0(0)	1(7.7)	9(69.2)	0.075	9	3(33.3)	0.325	8	2(25)	2(25)	1(12.5)	0.351
No	53	5(9.4)	4(7.5)	0(0)	44(83)		33	8(22.2)		41	11(26.8)	2(4.9)	2(4.9)	
aPLs,														
Yes	18	4(22.2)	2(11.1)	0(0)	12(66.7)	0.359	12	2(16.7)	0.637	12	2(16.7)	0(0)	2(16.7)	0.084
No	48	5(10.4)	2(4.2)	1(2.1)	40(83.3)		39	9(23.1)		36	10(27.8)	4(11.1)	1(2.8)	
High DNA														
Yes	21		2(9.5)	0(0)	19(90.5)	0.613	19	6(31.6)	0.252	21	7(33.3)	2(9.5)	0(0)	0.102
No	22		2(9.1)	1(4.5)	19(86.4)		19	3(15.8)		22	3(13.6)	2(9.1)	3(13.6)	
Low C3														
Yes	6		2(33.3)	0(0)	4(66.7)	0.095	4	2(50)	0.205	6	3(50)	2(33.3)	0(0)	0.361
No	36		2(5.6)	1(2.8)	33(91.7)		33	7(21.2)		36	6(16.7)	2(5.6)	3(8.3)	
Low C4														
Yes	4		1(25)	0(0)	3(75)	0.521	3	0(0)	0.306	4	1(25)	1(25)	0(0)	0.602
No	38		3(7.9)	1(2.6)	34(89.5)		34	9(26.5)		38	8(21.1)	3(7.9)	3(7.9)	
Protinurea														
Yes	16		2(12.5)	1(6.3)	13(81.2)	0.251	9	4(44.4)	0.414	16	4(25)	3(18.8)	1(6.2)	0.497
No	25		1(4)	0(0)	24(96)		24	5(20.8)		25	6(24)	1(4)	1(4)	
Low Platelet														
Yes	2		1(50)	0(0)	1(50)	0.039	1	0(0)	0.591	2	0(0)	1(50)	0(0)	0.178
No	44		2(4.5)	1(2.3)	41(93.2)		39	9(23.1)		44	11(25)	3(6.8)	2(4.5)	

*P-values were computed using Chi-square, Fisher Exact and Yates corrected Chi-square test.
**Total number in each section may not be equal to 69 as some of the data are not available for the review or miscarriages were excluded.
†N not equal to sum of IUGR, Eclampsia and preeclampsia due to omission of other complication.

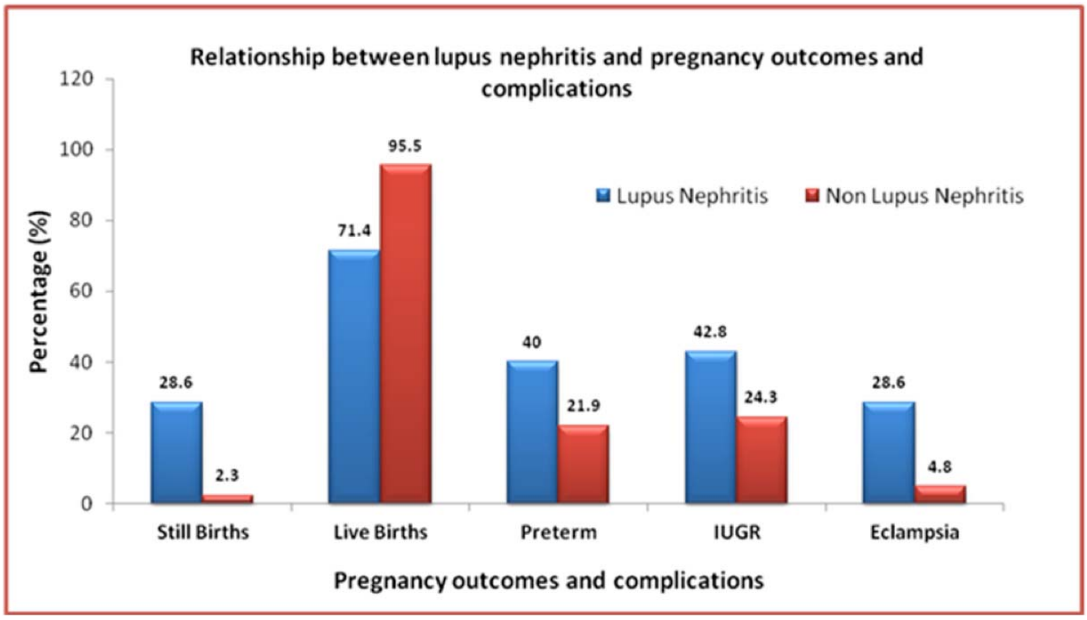

Figure 1: Relation between lupus nephritis and pregnancy outcomes.

with higher rate of stillbirth, IUGR, preterm delivery, and PIH, however, the differences were not statistically significant (p>0.05) (Table **3**, Figure **1**).

Relationship of Pregnancy Outcomes with Different SLE Features by Logistic Regression Analysis

Factors that were analyzed to identify the predictors of pregnancy outcomes (live birth, preterm births, IUGR) included LN, anti-Ro antibodies, anti-La antibodies, aPLs, anti-ds DNA, proteinuria and C3.

Results indicated that LN (OR 8.4; 95% CI 0.96-73.4; p=0.054), aPLs (OR 2.5; 95% CI 0.72-8.7; p=0.147), proteinuria (OR 5.5; 95% CI 0.52-58.6; p=0.155) and low C3 (OR 5.5; 95% CI 0.69-43.5; p=0.106) were potential (p<0.15) adverse predictors for live births. Anti-Ro antibodies (OR 3.3; 95% CI 0.83-12.9; p=0.091), anti-ds DNA (OR 2.5; 95% CI 0.51-11.8; p=0.260), and low C3 (OR 3.7; 95% CI 0.44, 31.3; p=0.227) were strongly associated with preterm live births and anti-Ro antibodies (OR 4.1; 95% CI 1.2-14.8; p=0.029) were significantly associated with IUGR (Table **4**). LN, anti-La antibodies, high anti-ds DNA, and low C3 were potential predictors for IUGR, however these differences were not statistically significant (p>0.05). Using multivariable logistic regression analysis controlling for all other potential predictors and covariates such as LN, anti-Ro antibodies, anti-La antibodies, aPLs, anti-ds DNA, proteinuria and C3, we found that the factors absence of LN was strongly associated with live births (adjusted OR 7.8; 95% CI 0.84-71.3; p=0.071) and anti-Ro antibodies was significantly associated with IUGR (adjusted OR 6.6; 95% CI 1.3-32.5; p=0.020).

DISCUSSION

In our cohort of SLE, the majority of patients had a successful pregnancy outcome with 78.3% having a live birth, which is comparable to other studies in developing countries (India 50% Thailand 89.7% Brazil 81.6% Egypt 77.8%) [10-12, 27]. We observed no significant differences in pregnancy outcomes between women who are in remission at conception and those with active SLE, but without renal involvement. However the patients who had active LN had worse pregnancy outcomes. This result support the recommendation of conception should be during remission of disease especially inactive LN.

Previous studies have shown increased adverse pregnancy outcome associated with SSA and SSB positivity [13-15]. In these studies preterm delivery and IUGR were increased with positive SSA and SSB. Our study showed SSA positivity were significantly associated with IUGR and strongly associated with preterm birth (p=0.227). However, other studies did not show significant associations between SSA and SSB positivity and adverse pregnancy outcomes [16-18].

A prospective study analysing pregnancy outcome in SLE, has shown that fetal loss and IUGR correlate with the absence of anti-Ro/SSA antibodies [20].

Though not significant, high anti-ds DNA in our study is strongly associated with preterm birth which

Table 4: Relationship of Pregnancy Outcomes with Different SLE Features

Predictors	Live Births		Preterm Live Births		IUGR	
	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Lupus Nephritis						
Yes	1.0	0.054	2.4 (0.34,16.4)	0.382	2.1 (0.41, 10.9)	0.373
No	8.4 (0.96, 73.4)		1.0		1.0	
Anti-Ro antibodies						
Yes	1.0	0.761	3.3 (0.83, 12.9)	0.091	4.1 (1.2, 14.8)	0.029
No	1.2 (0.35, 4.3)		1.0		1.0	
Anti-La antibodies						
Yes	1.0	0.270	2.2 (0.45, 10.7)	0.333	1.6 (0.34, 7.4)	0.555
No	2.2 (0.55, 8.6)		1.0		1.0	
aPL						
Yes	1.0	0.147	1.5 (0.28, 8.1)	0.638	0.57 (0.11, 2.9)	0.500
No	2.5 (0.72, 8.7)		1.0		1.0	
High DNA						
Yes	1.0	0.676	2.5 (0.51, 11.8)	0.260	1.9 (0.45, 7.8)	0.388
No	0.67 (0.1, 4.5)		1.0		1.0	
Proteinuria						
Yes	1.0	0.155	1.9 (0.4,8.9)	0.418	0.9 (0.21, 3.7)	0.866
No	5.5 (0.52, 58.6)		1.0		1.0	
Low C3						
Yes	1.0	0.106	3.7 (0.44, 31.3)	0.227	3.7 (0.61, 22.6)	0.154
No	5.5 (0.69, 43.5)		1.0		1.0	

OR: odds ratio; CI: confidence interval; aPL: antiphospholipid antibodies
For dichotomous outcome variables live births, preterm live births and IUGR, the reference category is taken as 'No'. For all the predictor variables the reference category are taken as "No" except for predictors corresponds to dichotomous outcome variable live births in which the reference category for the predictive variables are taken as 'Yes'.

was shown in previous study [18]. In other studies anti-ds DNA positivity was associated with a higher rate of pregnancy loss and preeclampsia [15, 18].

Similar to the presence of anti-Ro and high levels of anti-ds DNA, low levels of C3 is strongly associated with adverse pregnancy outcomes, mainly preterm birth. However, previous study did not show any significant association between low C3 and preterm delivery [16].

It has been estimated that women with SLE have fewer live births compared with the general population, in particular those with high disease activity [24]. LN, aPL, proteinuria and low C3 were potential ($p<0.15$) adverse predictors for live births in our study. A study on Japanese population showed significantly low live births in patients with low complements and antiphospholipid syndrome [25].

Another study on Chinese population showed a significant relation between proteinuria and fetal loss. Some studies have shown that there is no significant incidence of fetal loss in patients with LN [24, 25, 26].

There are significant variations in the percentage of live births in Asian countries, ranging from 45% (India) [22] to 91.6% (Taiwan) [23]. Improvements in disease management and perinatal monitoring have resulted in a significant decrease in pregnancy loss in SLE over the last few decades. The rate of loss in SLE pregnancies over the past 40 years decreased from a mean of 43% in 1960-1965 to 17% in 2000-2003. These advances highlight the importance of collaboration between rheumatologists and perinatologists [21].

In our study we observed better maternal and fetal outcomes. This could partly be due to early follow up and management of pregnant women with SLE in our specialized pregnancy clinic since it results in the early diagnosis of active lupus patients and advice to delay pregnancy until the disease is quiescent. This also highlights the importance of pre-pregnancy counseling of women with SLE.

The limitations of this study include its small sample size and its retrospective observational design. Finally,

the impact of SLE on pregnancy outcomes was not compared with the pregnancy outcome of the general population. A large comparative study between pregnancies in lupus patients and the general population is required. Case control study design with SLE and non-SLE patients would provide a higher level of evidence on the determination of risk factors related to adverse pregnancy outcomes.

In summary, lupus patients are a high-risk pregnancy group. The potential risks may be decreased by planned pregnancy and the optimization of therapy prior to conception. In particular, preserved renal function prior to pregnancy may result in favorable outcomes even in patients who have a history of LN. Collectively, planned pregnancy and the evaluation of risk factors attributable to adverse fetal and maternal outcomes, such as proteinuria during pregnancy or the presence of antiphospholipid antibodies, is crucial in lupus patients. Better management and multidisciplinary care have meant that successful pregnancies are becoming the rule rather than exception in SLE. All lupus pregnancies should be considered high-risk and should be closely monitored. Patient education is crucial for a successful pregnancy outcome.

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CONFLICT OF INTEREST

Authors declare no conflict of interest and that the study has met institutional review board approval.

AUTHOR CONTRIBUTIONS

Principal investigators: Abdul Razzakh Poil and Samar Al Emadi.

Co-investigators: Mohammed Hammoudeh, Prem Chandra, Abdo Lutf.

Statistical analysis: Prem Chandra

NOTE

Part of this work was presented in American College of Rheumatology (ACR) annual meeting, San Diego, 2013 (Presentation Number: 2528).

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