ORIGINAL ARTICLE

Predictors of adverse pregnancy outcome in a cohort of women with systemic lupus erythematosus in Malaysia

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ABSTRACT

Introduction: Pregnancy in women with systemic lupus erythematosus (SLE) is known to be associated with adverse pregnancy outcomes (APO). We aimed to determine the frequency of APO, the associated variables and predictors.

Materials and Methods: This retrospective study included all pregnancies seen at the SLE Clinic, Kuala Lumpur Hospital from January 2008 to May 2020. Maternal outcomes included SLE flare during pregnancy, preeclampsia and eclampsia. Foetal outcomes included foetal loss, preterm birth and small-for-gestational age (SGA) neonates. Clinical and laboratory variables were examined. Variables from univariate analysis were entered into logistic regression model. Odds ratio and 95% confidence interval were reported.

Results: Of the 131 pregnancies, 106 (80.9%) were live births. Twenty-six (24.5%) babies were born preterm and 35 (33%) neonates were SGA. Twenty-four (18.3%) women had disease flare during pregnancy, with the majority (22/24) being mild to moderate flares. Four women experienced preeclampsia while none had eclampsia. Predictors of adverse maternal outcomes included high SLEDAI-2K score, proteinuria and hypocomplementemia within 6 months before conception and during pregnancy; history of lupus nephritis (LN), pre-existing hypertension, antiphospholipid syndrome (APS), antiphospholipid antibodies, anti-Ro antibody and anti-RNP antibody. Predictors of adverse foetal outcomes comprised APS, preeclampsia, anti-Sm antibody, history of neuropsychiatric systemic lupus erythematosus (NPSLE) and azathioprine use.

Conclusion: Pregnancy in SLE women is best deferred until disease activity is in remission for at least 6 months before conception. A history of LN is associated with a 3-fold risk of renal flare during pregnancy. Haematological abnormalities are rare in disease flare during pregnancy.

KEYWORDS:
Predictors, maternal, foetal, outcomes, systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which involves multiple organ systems and occurs predominantly in women of reproductive age. Fertility is generally not affected.[1] However, cyclophosphamide therapy used in the treatment of SLE has been known to affect gonadal function.[2] Pregnancy and its complications remain a concern to women with SLE as well as physicians who treat them given the fact that SLE has been shown to have significant impact on maternal and foetal outcomes.[3] Women with SLE are at significantly higher risk for foetal loss, preterm birth, preeclampsia and caesarean section when compared to women without SLE.[3-5] With increased understanding of the pathogenesis of SLE and improved treatment, higher rates of live births have been observed in women with SLE.[6] Identification of clinical and laboratory parameters that predict adverse pregnancy outcomes (APO) is vital to facilitate preconception counselling and management of SLE to ensure a favourable outcome for both mother and foetus. Therefore, we conducted this study to examine the frequency of APO, the clinical and laboratory parameters that are associated with APO, and the predictors of APO.

MATERIALS AND METHODS

This retrospective study included all pregnancies that occurred in women who attended the SLE clinic of Kuala Lumpur Hospital between January 2008 to May 2020. All patients fulfilled the American College of Rheumatology (ACR) 1997 revised classification criteria for SLE.[7] Exclusion criteria were patients who had ectopic pregnancies, induced abortions; and patients who had incomplete medical records. Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia. This study was also registered with the National Medical Research Register (NMRR-19-1232-48342).

Medical records of patients were systematically reviewed and data obtained. The following variables were recorded: demographic data; duration of SLE; associated antiphospholipid syndrome (APS); SLE activity within 6 months before conception and during pregnancy; gravidity and parity; presence of preeclampsia; outcome of pregnancy; gestational age; mode of delivery; indication for caesarean section; birth weight; duration of stay in neonatal intensive care unit (NICU); congenital heart block (CHB); medications received during pregnancy; pre-existing hypertension; history of LN, NPSLE and haematological manifestations. Laboratory parameters documented were full blood count, complement 3 (C3), complement 4 (C4), proteinuria; autoantibodies which

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included antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-Sm antibody, anti-Ro antibody, anti-La antibody, anti-ribosomal P antibody, anti-ribonucleoprotein (anti-RNP) antibody, lupus anticoagulant (LAC), anticardiolipin antibody (ACL) and anti-beta2 glycoprotein I antibody (anti-b2GPI).

Maternal outcomes included (1) disease flare during pregnancy, (2) preeclampsia and (3) eclampsia. SLE Disease Activity Index 2000 (SLEDAI-2K)[8] was used to evaluate disease activity of patients with SLE within 6 months before conception and during pregnancy. SLEDAI-2K score of ≥4 was defined as active phase of SLE. Mild to moderate disease activity was defined as SLEDAI-2K score of between 4 to 12. A score of >12 was considered severe disease activity.

Hypertension was defined as systolic blood pressure of 140 mm Hg or greater, or diastolic blood pressure of 90 mm Hg or greater. Preeclampsia was defined as the presence of hypertension and proteinuria of 0.3 g or greater in a 24-hour urine sample in patients with normal blood pressure and no evidence of proteinuria prior to 20 weeks of gestation. Eclampsia was defined as new onset of grand mal seizure activity and/or unexplained coma during pregnancy or postpartum in a woman with signs or symptoms of preeclampsia.

Foetal outcomes included (1) foetal loss, (2) small-for-gestational age (SGA) neonates and (3) preterm birth. Foetal loss was defined as the loss of pregnancy as a result of spontaneous abortion or stillbirth. Spontaneous abortion refers to spontaneous loss of the foetus before 20 weeks of gestation. Stillbirth was defined as the death of the foetus in utero above 20 weeks of gestation. Therapeutic abortion was defined as termination of pregnancy for medical indications. SGA was defined as birth weight below the tenth percentile for the gestational age. Preterm birth was defined as birth of a baby before 37 weeks of gestation.

Statistical analysis

In terms of analysis, each pregnancy was considered as an individual observation. Categorical variables were described in frequencies and percentages; while continuous variables were reported in means and standard deviations (SD), or medians and interquartile ranges (IQR). Fisher's exact test was used to analyse the significance of association between each variable and adverse outcome. Two-sided $p<0.05$ was considered statistically significant. Variables with a p-value of <0.05 from the univariate analysis were entered into a logistic regression model. Odds ratio (OR) and 95% confidence interval (CI) were reported.

RESULTS

A total of 131 pregnancies in 93 women were identified. Sixty-eight (73.1%) women had 1 pregnancy, 17 (18.3%) two pregnancies, four (4.3%) three pregnancies, three (3.2%) four pregnancies and one (1.1%) five pregnancies. There were 79 Malays (85.0 %), 9 (9.7%) Chinese and 5 (5.3%) Indians. Fifteen (11.5%) women had concomitant APS; while 4 (4.3%) had overlap syndrome, of whom 3 had rheumatoid arthritis and one had systemic sclerosis. Mean age at disease onset was 24.0 (SD 5.3) years and mean age at conception was 29.6 (SD 4.5) years. With regard to disease activity, the majority (84.3%) of women had inactive disease within 6 months before conception. SLE was diagnosed during pregnancy in 4 (3.1%) women. A history of LN was observed in 17 (13.0%) women while 8 (6.1%) women had pre-existing hypertension. Table I summarizes the baseline clinical characteristics and laboratory features of our patient cohort.

Of the 131 pregnancies, prednisolone was used in 113 (86.3%) pregnancies and hydroxychloroquine in 116 (88.5%) (Table II). Majority (93.9%) of women received aspirin. Low-molecular-weight heparin (LMWH) was prescribed to 13 of the 15 women with secondary APS. The remaining two women suffered miscarriages very early into the first trimester of pregnancy before their appointment at the SLE clinic. Hence treatment with LMWH was not initiated.

Foetal outcomes

There were 106 (80.9%) live births. Twenty-one (16.0%) pregnancies ended in spontaneous abortions and 3 (2.3%) were stillbirths. One (0.8%) woman underwent therapeutic termination of pregnancy in view of proteinuria and deterioration in renal function (Table III). Majority (22/25, 88%) of the spontaneous abortions occurred in the first trimester and early second trimester.

With regards to the 106 live births, mean gestational age at birth was 37.3 (SD 3.5) weeks (range 30.1 to 41.1). Twenty-six (24.5%) babies were born preterm. Mean birth weight was 2.60 (SD 0.49) kg and 35 (33.0%) neonates were SGA.

Fifty-two (49.1%) babies were delivered via vaginal route while the remaining 54 (50.9%) by caesarean section. The leading cause for caesarean section was failed induction of labour, as observed in 12 (32.4%) cases. This was followed by foetal distress in 11 (29.7%) cases and poor progress of labour in 7 (18.9%) cases. Three (8.1%) women had preterm premature rupture of membranes and 2 (5.4%) had preeclampsia.

There were no cases of neonatal death, foetal congenital heart block (CHB) or neonatal lupus erythematosus. Thirty-seven neonates were admitted to NICU. The duration of NICU stay ranged from one to 60 days.

Maternal outcomes

Twenty-four (18.3%) women experienced disease flare during pregnancy, of whom 22 (16.8%) had mild to moderate flare while 2 (1.5%) had severe flare (Table II). The mean SLEDAI-2K score for the aforementioned 24 women was 6.0 (SD 3.3). Twelve (50%) women had malar rash and 11 (45.8%) had proteinuria. Five (45.4%) of the 11 women with proteinuria had a history of LN. Haematological abnormality occurred in one woman, who had thrombocytopenia. All the women with disease flare received escalation in prednisolone dosage. Azathioprine was introduced in 6 women, all of whom had renal flare. The median dosage of prednisolone was 15 (IQR 10) mg daily, and the highest dose received was 60 mg daily. Four women developed preeclampsia, while none had eclampsia (Table III).

Table I: Baseline clinical and laboratory features

CHARACTERISTICS	NUMBER (%) n=131	MEAN (SD)	MEDIAN (IQR)
Age at disease onset (years)		24.0 (5.3)	
Age at conception (years)		29.6 (4.5)	
Duration of SLE (months)			72.0 (77.0) Range 0 to 268
Antiphospholipid syndrome	15 (11.5)		
Concomitant connective tissue disease	4 (3.1)		
Pre-existing hypertension	8 (6.1)		
History of lupus nephritis	17 (13.0)		
History of NPSLE	7 (5.3)		
History of thrombocytopenia	33 (25.2)		
History of leukopenia	47 (35.9)		
History of autoimmune haemolytic anaemia	12 (9.2)		
Autoantibodies			
Anti-dsDNA positivity (n=128)	62 (48.4)		
Anti-Sm antibody positivity (n=129)	37 (28.7)		
Anti-Ro antibody positivity (n=129)	66 (51.6)		
Anti-La antibody positivity (n=129)	27 (20.9)		
Anti-RNP antibody positivity (n=129)	34 (26.4)		
Anti-ribosomal P antibody positivity (n=129)	25 (19.4)		
Lupus anticoagulant positivity (n=57)	17 (29.8)		
Anticardiolipin antibody positivity (n=121)	13 (10.7)		
Anti-beta2-glycoprotein I antibody positivity (n=61)	6 (9.8)		

Table II: Patient characteristics within 6 months before conception and during pregnancy

Characteristics	Within 6 months before conception n=115*(%)	During pregnancy n=131(%)
SLEDAI-2K		
SLEDAI-2K unknown	16	0
SLEDAI-2K <4	97 (84.3)	107 (81.7)
SLEDAI-2K ≥4	18 (15.7)	24 (18.3)
SLEDAI-2K 4 to 12	16 (13.9)	22 (16.8)
SLEDAI-2K >12	2 (1.7)	2 (1.5)
SLE clinical manifestations		
Malar rash	9 (7.8)	12 (9.2)
Oral ulcers	6 (5.2)	3 (2.3)
Arthritis	4 (3.5)	4 (3.1)
Low complement 3	24 (20.9)	22 (16.8)
Low complement 4	14 (12.2)	17 (13.0)
Proteinuria	6 (5.2)	11 (8.4)
NPSLE	0 (0)	0 (0)
Thrombocytopenia	4 (3.5)	1 (0.8)
Leukopenia	2 (1.7)	0 (0)
Autoimmune haemolytic anaemia	0 (0)	0 (0)
Medications		
Prednisolone		113 (86.3)
Hydroxychloroquine		116 (88.5)
Aspirin		123 (93.9)
Low-molecular-weight heparin		13 (9.9)
Azathioprine		22 (16.8)

*n=115 as the status of 16 women with SLE were unknown within 6 months before conception because they presented to the SLE clinic when they were already pregnant, or had new-onset SLE at pregnancy.

Predictors of adverse maternal outcome

Univariate analysis demonstrated the following factors to be associated with adverse maternal outcomes. High SLEDAI-2K score within 6 months before conception, history of LN, hypocomplementemia within 6 months before conception and during pregnancy, proteinuria within 6 months before conception and during pregnancy, and anti-Ro antibody positivity were predictors of disease flare during pregnancy. APS, pre-existing hypertension, anti-RNP antibody positivity, LAC positivity, ACL positivity and proteinuria within 6 months before conception were significantly predictive of preeclampsia. Table IV summarizes the results of the univariate analysis.

Table III: Adverse maternal and foetal outcomes

	Number (%)
Adverse maternal outcome	
Flare during pregnancy (n=131)	24 (18.3)
Preeclampsia (n=109)	4 (3.7)
Eclampsia (n=109)	0 (0)
Adverse foetal outcome	
Foetal loss (n=131)	25 (19.1)
- Spontaneous abortion	21 (16.0)
- Stillbirth	3 (2.3)
- Termination of pregnancy	1 (0.8)
Preterm birth (n=106)	26 (24.5)
SGA (n=106)	35 (33.0)

Table IV: Variables associated with adverse maternal outcomes

	Flare during pregnancy		Preeclampsia	
	p value	OR (95% CI)	p value	OR (95% CI)
APS	0.727	1.20 (0.31,4.65)	0.007*	10.67 (1.34, 85.01)
SLEDAI-2K ≥4 within 6 months before conception	0.000*	23.00 (6.31, 83.89)	0.507	1.81 (0.18, 18.67)
History of lupus nephritis	0.039*	3.11 (1.02, 9.54)	0.428	2.36 (0.23, 24.40)
Pre-existing hypertension	0.146	3.09 (0.68, 13.98)	0.020*	20.00 (2.33, 172.72)
History of NPSLE	0.353	0.82 (0.75, 0.89)	1.000	0.96 (0.93, 0.99)
Haematological abnormalities within 6 months before conception	0.070	0.41 (0.16, 1.07)	1.000	1.06 (0.14, 7.80)
Anti-dsDNA	0.364	0.63 (0.25, 1.58)	1.000	1.08 (0.15, 7.98)
Anti-Sm antibody	0.197	1.95 (0.75, 5.07)	1.000	1.04 (0.10, 10.45)
Anti-Ro antibody	0.037*	2.93 (1.06, 8.06)	1.000	1.02 (0.14, 7.52)
Anti-La antibody	0.404	0.52 (0.14, 1.90)	1.000	1.04 (0.10, 10.45)
Anti-Ribosomal P antibody	0.597	1.38 (0.51, 3.75)	0.573	0.95 (0.91, 0.99)
Anti-RNP antibody	0.684	1.50 (0.32, 7.14)	0.022*	1.30 (0.97, 1.75)
Lupus anticoagulant	1.000	1.00 (0.26, 3.84)	0.022*	8.00 (1.02, 62.63)
Anticardiolipin antibody	0.253	2.94 (0.46, 18.79)	0.023*	30.00 (2.08, 433.13)
Anti-beta2 glycoprotein I antibody	0.137	2.81 (0.82, 9.61)	1.000	0.95 (0.91, 0.99)
Low C3 within 6 months before conception	0.004*	5.58 (1.78, 17.46)	1.000	1.33 (0.13, 13.59)
Low C4 within 6 months before conception	0.003*	7.67 (2.17, 27.04)	1.000	0.95 (0.91, 0.99)
Haematological abnormality within 6 months before conception	1.000	0.87 (0.81, 0.93)	1.000	0.96 (0.92, 0.99)
Proteinuria within 6 months before conception	0.003*	17.82 (2.92, 108.68)	0.036*	9.67 (0.76, 122.45)
Low C3 during pregnancy	0.000*	10.69 (3.76, 30.41)	0.498	1.85 (0.18, 18.96)
Low C4 during pregnancy	0.000*	22.47 (6.67, 75.70)	1.000	0.96 (0.92, 0.99)
Haematological abnormality during pregnancy	1.000	0.96 (0.93, 0.99)	1.000	0.96 (0.93, 0.99)
Proteinuria during pregnancy	0.000*	82.31 (9.74, 695.88)	0.295	4.04 (0.38, 43.46)

*denotes significant p value of <0.05; APS – antiphospholipid syndrome; SLEDAI – systemic lupus erythematosus disease activity index; NPSLE – neuropsychiatric systemic lupus erythematosus; OR – odds ratio; CI – confidence interval

Predictors of adverse foetal outcomes

Table V depicts the results of adverse foetal outcomes. APS, preeclampsia and anti-Sm antibody positivity were associated with foetal loss. Azathioprine use was associated with SGA neonates, and a history of NPSLE was related to preterm birth.

DISCUSSION

In spite of multiple risk factors that have been shown to have impact on pregnancy outcomes in women with SLE, a large proportion of women essentially have favourable outcomes. Analysis of our data demonstrated that lupus flare within 6 months before conception was significantly associated with a 23-fold increased risk of disease flare during pregnancy. This observation is consistent with previous studies.[9-11] Of note, the majority (22/24, 91.7%) of disease flares during pregnancy were mild to moderate in activity, while 8.3% were severe flares. The organs more frequently affected in lupus flares were the skin, joints and kidneys, similar to the observation by Petri.[12] Only one woman in our cohort had haematological abnormality, that was, thrombocytopenia. Interestingly, we did not observe any lupus flare that manifested with leukopenia or haemolytic anaemia. Therefore, our study suggested that haematological abnormalities are rare during pregnancy flares. We found that hypocomplementemia and proteinuria within 6 months before conception were predictive of disease flare during pregnancy. C3 and C4 are useful biomarkers in monitoring disease activity in SLE, and they are also used to distinguish exacerbation of disease activity from preeclampsia during pregnancy.[13] Hypocomplementemia is well recognized as an indicator of active disease, in particular, LN.[14] Likewise, the presence of proteinuria is a sign that represents active LN.

Our data also identified hypocomplementemia during pregnancy as a predictor of lupus flare during pregnancy. In normal pregnancy, complement levels are known to rise,

Table V: Variables associated with adverse foetal outcomes

	Foetal loss		SGA		Preterm birth	
	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)
APS	0.040*	3.40 (1.08, 10.69)	0.715	0.55 (0.11, 2.82)	0.686	1.61 (0.37, 6.95)
SLEDAI-2K ≥4 within 6 months before conception	0.756	1.17 (0.35, 3.97)	1.000	0.85 (0.24, 2.96)	1.000	0.79 (0.20, 3.13)
Preeclampsia	0.006*	17.17 (1.20, 244.62)	0.209	1.45 (0.37,48.48)	0.148	6.58 (0.57, 75.79)
History of lupus nephritis	0.740	1.36 (0.40, 4.60)	0.755	1.31 (0.39, 4.35)	1.000	0.91 (0.23, 3.61)
Pre-existing hypertension	0.648	1.45 (0.28, 7.65)	0.661	0.39 (0.04, 3.46)	0.634	1.58 (0.27, 9.19)
History of NPSLE	1.000	0.694 (0.08, 6.04)	1.000	1.02 (0.18, 5.83)	0.031*	7.09 (1.22, 41.30)
Haematological abnormalities within 6 months before conception	0.385	0.67 (0.28, 1.62)	1.000	0.88 (0.35, 2.21)	1.000	1.00 (0.41, 2.42)
Anti-dsDNA	0.824	0.88 (0.36, 2.14)	0.535	1.37 (0.61, 3.11)	0.822	0.86 (0.35, 2.09)
Anti-Sm antibody	0.026*	2.92 (1.18, 7.21)	0.473	1.44 (0.57, 3.65)	1.000	0.93 (0.33, 2.66)
Anti-Ro antibody	0.191	1.85 (0.75, 4.56)	0.300	1.63 (0.72, 3.71)	0.653	1.29 (0.53, 3.15)
Anti-La antibody	0.280	0.43 (0.12, 1.56)	0.231	1.80 (0.72, 4.54)	0.428	1.59 (0.59, 4.30)
Anti-Ribosomal P antibody	0.127	2.22 (0.89, 5.58)	0.633	1.25 (0.48, 3.22)	1.000	1.00 (0.35, 2.87)
Anti-RNP antibody	0.738	1.44 (0.39, 5.16)	0.711	1.44 (0.34, 6.09)	1.000	1.05 (0.26, 4.33)
Lupus anticoagulant	1.000	1.00 (0.26, 3.84)	0.745	0.70 (0.17, 2.84)	0.136	2.88 (0.79, 10.41)
Anticardiolipin antibody	0.106	2.56 (0.46, 18.79)	1.000	0.50 (0.05, 5.19)	1.000	0.67 (0.06, 6.97)
Anti-beta2 glycoprotein I antibody	1.000	0.82 (0.17, 4.02)	0.515	1.58 (0.44, 5.63)	0.265	2.15 (0.56, 8.21)
Low C3 within 6 months before conception	0.268	1.79 (0.64, 5.02)	0.258	2.02 (0.70, 5.82)	0.767	1.19 (0.38, 3.82)
Low C4 within 6 months before conception	0.295	0.28 (0.03, 2.23)	0.539	1.43 (0.43, 4.83)	0.730	1.40 (0.39, 5.08)
Haematological abnormality within 6 months before conception	1.000	0.79 (0.73, 0.88)	1.000	0.79 (0.73, 0.88)	1.000	0.75 (0.66, 0.84)
Proteinuria within 6 months before conception	0.093	4.45 (0.84, 23.69)	1.000	1.09 (0.09, 12.52)	1.000	1.52 (0.13, 17.62)
SLEDAI-2K ≥4 during pregnancy	0.771	1.22 (0.41, 3.69)	0.796	0.85 (0.24, 2.97)	0.738	0.79 (0.20, 3.13)
Low C3 during pregnancy	0.370	1.78 (0.62, 5.13)	0.151	2.33 (0.79, 6.86)	0.214	2.10 (0.68, 6.49)
Low C4 during pregnancy	1.000	0.89 (0.24, 3.39)	0.221	2.29 (0.73, 7.13)	0.324	1.88 (0.57, 6.22)
Haematological abnormality during pregnancy	1.000	0.81 (0.74, 0.88)	1.000	1.02 (0.09, 11.59)	1.000	1.56 (0.14, 17.94)
Proteinuria during pregnancy	0.438	1.67 (0.41, 6.81)	0.435	2.16 (0.51, 9.21)	0.099	3.46 (0.79, 14.95)
Azathioprine use	0.284	1.78 (0.62, 5.13)	0.044*	3.17 (1.07, 9.39)	1.000	1.03 (0.30, 3.52)

*denotes significant p value of <0.05

likely due to increased hepatic synthesis from the influence of oestrogen. Falling levels of complements during pregnancy, albeit within the normal range, have been shown to be associated with increased lupus activity.[13] Davis-Porada et al[15] identified low C4 level to be predictive of flare during pregnancy from the PROMISSE (Predictors of pregnancy outcome: biomarker in antiphospholipid antibody syndrome and systemic lupus erythematosus) study.[16]

Our cohort revealed that a history of LN was significantly associated with lupus flare during pregnancy, with an OR of 3.1 (95% CI: 1.02, 9.54). Similar conclusions were noted from earlier studies.[10,17-19] Therefore, it is crucial to closely monitor women who had a previous history of LN and include mandatory urinalysis at every follow-up visit during the antenatal period in order to promptly recognise a renal flare and avoid serious complications.

Univariate analysis in our study showed that anti-Ro antibody positivity had a significant correlation with lupus flare during pregnancy. This association has not been reported in the literature, mainly because this aspect has not been examined. Anti-Ro antibodies are known to be associated with neonatal lupus and CHB. The prevalence of CHB in the offspring of an anti-Ro antibody positive woman was reported as 2%.[20] Of note, there were no cases of CHB in our cohort. A possible explanation is that a vast majority (88.5%) of our patients received hydroxychloroquine during pregnancy. Over the past couple of decades, hydroxychloroquine has emerged as the cornerstone of SLE therapy. Its widespread use among pregnant women with SLE was derived from studies that demonstrated the benefit of hydroxychloroquine in preventing lupus flares during pregnancy.[9,21,22] In addition, a study by Izmirly et al[23] which involved databases from 3 countries reported that hydroxychloroquine use during pregnancy was associated with a decreased risk of cardiac neonatal lupus, indicating a protective effect. Unfortunately, the exact mechanism of how hydroxychloroquine exerts this effect remains to be elucidated.

Our data showed that the predictors for preeclampsia were APS, lupus anticoagulant positivity, ACL positivity, pre-existing hypertension, proteinuria within 6 months before conception and anti-RNP antibody positivity. Previous studies[24-26] had demonstrated similar associations wherein APS and antiphospholipid antibodies were positively linked to preeclampsia. Our findings suggest that patients with APS, as well as patients without APS but positive for antiphospholipid antibodies should be closely monitored for detection of preeclampsia.

Pre-existing hypertension and proteinuria within 6 months before conception were demonstrated as predictive factors for

preeclampsia in our cohort. Likewise, these findings were consistent with results from a population-based case control study conducted by Davies et al[27] which confirmed that pre-existing hypertension predisposed a woman to preeclampsia, and women who developed preeclampsia had a higher prevalence of pre-existing renal disease.

Reports from multiple studies have shown that foetal loss among SLE women varied widely from 3.9%[10,16] to 38.5%.[17,28,29] Overall, the rate of foetal loss in the general population is approximately 10 to 20%. The frequency of foetal loss in our cohort was 19.1%, which comprised spontaneous abortion in the first trimester and early second trimester. The predictors for foetal loss that were identified were APS, preeclampsia and anti-Sm antibody positivity. Our findings concurred with several studies[10,28,30] which demonstrated APS to be a risk factor for foetal loss. Nonetheless, our study showed that antiphospholipid antibodies per se were not risk factors for foetal loss, unlike other reports.[21,31-34] Foetal loss was inevitable in some of our APS patients despite having received the recommended treatment with low-dose aspirin and LMWH from the first trimester of pregnancy. This suggests that placental thrombosis is not the main aetiology in the pathogenesis of foetal loss. The exact mechanism of foetal loss in APS remains unclear, highlighting the need for further investigation into its pathogenesis in order to prevent obstetric APS.

We identified preeclampsia as a significant predictor for foetal loss, similar to conclusions drawn from a study by Liu et al.[35] Therefore, careful monitoring during the antenatal period is crucial for early detection and appropriate management of pregnancy-induced hypertension and preeclampsia.

Among the autoantibodies tested in our patients, anti-Sm antibody emerged as a risk factor for foetal loss. Interestingly, this association has not been reported. From our observation, the majority of studies which evaluated autoantibodies as predictors of adverse pregnancy outcomes did not include anti-Sm antibody in their analysis, having applied more emphasis on other autoantibodies, in particular, antiphospholipid antibodies. Therefore, we suggest to consider evaluation of anti-Sm antibody as a predictive factor for APO in future research.

Another foetal complication of SLE pregnancy is SGA neonates. The frequency of SGA neonates in our cohort was 33.0%, and the predictive factor identified was azathioprine use. Azathioprine was administered to patients with organ-threatening disease and those who had inadequate symptom control with hydroxychloroquine and prednisolone. Of the 17 women who received azathioprine prior to conception, the indication for 12(70.6%) of them was LN. Studies by Imbiascati et al[18] and Lacerda et al[36] found that a history of LN and active proliferative LN during pregnancy respectively, were associated with SGA neonates. Nevertheless, azathioprine per se has not been associated with low-birth-weight neonates.[37]

Preterm birth is a recognised complication of lupus pregnancies. The frequency of preterm birth in the general population was reported to be approximately 13.3%,[29] while preterm birth among women with SLE varied between 21.3% and 43.6%.[9,17] Meta-analysis by Bundhun et al[3] showed a significantly higher rate of preterm birth among women with SLE compared with women who did not have SLE, with a relative risk of 3.05 (95% CI: 2.56–3.63; p<0.01). The frequency of preterm birth in our cohort was 24.5%. The majority (61.5%) of preterm births occurred between 35 to 37 weeks of gestation, and premature rupture of membranes was noted to be the leading cause, comprising 69.2% of cases. Our study revealed a history of NPSLE as predictor for preterm birth, as described by de Jesús et al.[38]

With regard to medication, 93.9% of our SLE patients received low-dose aspirin during pregnancy. Aspirin is recommended and frequently prescribed for SLE patients during pregnancy for prevention of preeclampsia[39] given the greater risk of preeclampsia in pregnant women with SLE as opposed to women without SLE. In patients with concomitant APS, they received a combination of aspirin and heparin. It is conceivable that the low rate of preeclampsia in our patients may be attributed to the high frequency of maternal exposure to aspirin, thus confirming its protective role.

As a comparison, we wish to highlight that the rates of preeclampsia and eclampsia in the East Malaysian cohort as reported by Teh et al[10] contrasted with ours (13.9% of cases with preeclampsia and 1.7% of cases with eclampsia vs. 3.7% of cases with preeclampsia and 0% of eclampsia). A striking observation and plausible contributing factor was the considerably lower rate of aspirin exposure (40.9% vs. 93.9%) among their patients.

We observed a high caesarean section rate of 50.9% in our cohort. Notably, the rate of caesarean section among women in Malaysia was reported as 23.2%.[40] This confirms that women with SLE encounter greater risk of complications during pregnancy, than women without SLE.

The limitations of our study are acknowledged. This research is retrospective in nature and involved a single site. Nevertheless, the strengths of our study include the relatively large sample size and evaluation of numerous clinical and laboratory variables. A positive point in this study as opposed to multi-centre trials is the uniformity and standardization of patient care and treatment, which accordingly impacts the provision of consistent statistics on patient management. Various risk factors have been identified as predictors of adverse pregnancy outcome in previous studies. Nonetheless, no common predictive factors have been consistently ascertained to date. This is probably attributed to the various study designs, case definitions, as well as management strategies in different centres. In addition, patient populations are diverse and studies have shown that SLE patients of various descent demonstrate differences in clinical manifestations and treatment response.

For the information of our readers, pre-pregnancy counselling is routinely conducted at our SLE clinic. Counselling on contraception and pregnancy is given to all newly-diagnosed SLE patients as well as follow-up patients who are in the reproductive age. Our patients are frequently

reminded that SLE activity has to be stable or quiescent prior to conception in order to ensure a successful pregnancy. It is clear that patient education and shared decision-making are crucial in ensuring a better control of disease and ultimately, a positive outcome.

In conclusion, pregnancies in SLE women are associated with an increased risk of maternal and foetal adverse outcomes. Women with SLE need to defer pregnancy until disease activity has been in remission for at least 6 months in order to minimise the risk of flare during pregnancy. A history of LN is associated with a 3-fold increased risk of renal flare during pregnancy. Haematological abnormalities rarely manifest during disease flare in pregnancy. Greater use of aspirin and hydroxychloroquine contributed to low rates of preeclampsia and CHB, respectively. In spite of numerous obstacles, favourable pregnancy outcomes can be achieved albeit with close monitoring during pregnancy, prompt intervention and multidisciplinary involvement.

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