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CLINICAL & BASIC RESEARCH

Pregnancy Outcomes in Systemic Lupus Erythematosus Women

A single tertiary centre experience

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abstract: ***Objectives:*** This study was conducted to assess pregnancy outcomes in women with systemic lupus erythematosus (SLE) in Oman. ***Methods:*** A retrospective cohort study of 149 pregnancies in 98 women with SLE was conducted over 10 years to evaluate the impact of clinical and laboratory parameters in predicting adverse pregnancy outcomes. ***Results:*** Mean maternal age was 30.6 ± 5 years ranging from 20–44 years, and the mean disease duration was 10 ± 5 years, ranging from 2–27 years. The most common maternal manifestations were joint pain in 36 (24.2%), lupus nephritis (LN) in 18 (12.08%), preeclampsia in 11 (7.4%), eclampsia in three (2%) and lupus flare in one pregnancy. The live birth rate was 139 (93.3%) with a mean gestational age of 36 ± 2 weeks ranging from 26–40 weeks. In total, 55 (39.6%) were preterm deliveries, six (4%) pregnancies ended in miscarriage, and four (2.7%) resulted in intrauterine fetal death. Intrauterine growth restriction was observed in 49 babies (35%). A significant association was found between hypertension (HTN) and miscarriage (P = 0.024) and preterm birth (P = 0.019). In addition, HTN was positively associated with preeclampsia (P = 0.004) and LN (P = 0.048). Antiphospholipid syndrome impacted preterm birth (P = 0.013) and postpartem haemorrhage (PPH) (P = 0.027) and was found to be a significant predictor for women developing deep vein thrombosis and pulmonary embolism (P <0.001 for both). ***Conclusion:*** Despite potential complications, most pregnancies complicated by SLE in Oman result in good outcomes. Adverse pregnancy outcomes, however, may still occur in women with SLE. In women with SLE, pregnancy planning, careful antenatal monitoring and efficient SLE treatment need to be undertaken for successful pregnancy outcomes.

Keywords: Systemic Lupus Erythematosus; Pregnancy Outcomes; Lupus Nephritis; Antiphospholipid Antibodies; Neonatal Lupus.

Advances in Knowledge

- *The live birth rate of SLE women was high and attributable to good disease control and patient care during pregnancy.*
- *Pregnancy complications were low and were mainly associated with chronic hypertension and antiphospholipid syndrome.*

Application to Patient Care

- *The findings of this study will increase obstetricians' awareness of SLE and help them improve counselling and care in patients with SLE.*
- *Controlling SLE activity and remission will help improve the outcomes for both mothers and neonates.*

Systemic lupus erythematosus (SLE) is a chronic, multi-system, connective tissue autoimmune disease which predominantly affects females of reproductive age. SLE is characterised by a pattern of remission and relapse and occurs in approximately one per 1,000 women.[1,2] The prevalence of SLE has increased in the last few years due to improvements in disease diagnosis. According to a retrospective cohort study conducted in the UK using Clinical Practice Research Data (CPRD) from between 1999 and 2012, the prevalence of SLE increased from 64.99/100,000 in 1999 to 97.04/100,000 in 2012.[3] Because more than 90% of cases of SLE occur in females of reproductive age, pregnancy is an important consideration in the progression of the disease.[4]

SLE's presentation varies from simple polyarthralgia with a rash to a multi-organ life-threatening affliction.[5,6] Fertility rates in women with SLE are not affected, but pregnancy in some circumstances can be associated with poor outcomes for both mother and fetus.[7,8] Pregnancy outcomes are usually affected by several factors in women with SLE, including the presence of previous lupus nephritis (LN), antiphospholipid (aPL) antibodies and maternal hypertension (HTN), and the exacerbation of lupus activity during pregnancy.[7]

Improvements in healthcare and medical discoveries in recent decades have improved SLE patients' quality of life (QOL) including pregnancy outcomes.[9] A systematic review and meta-analysis of pregnancy outcomes in patients with SLE and LN conducted by the American Society of Nephrology in 2010 included 37 studies with 1,842 patients and 2,751 pregnancies. The results showed that the most common maternal

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complications in pregnant women with SLE were lupus flare (26%), HTN (16%), nephritis (16%), preeclampsia (8%) and eclampsia (1%).[10] Fetal outcomes reported by the same study were spontaneous abortion (16%), neonatal death (3%), stillbirth (4%), intrauterine growth restriction (IUGR; 13%) and premature birth (39%). Finally, premature birth rate, active nephritis and increased HTN rates in patients with active nephritis or a history of nephritis were found to increase the risk of adverse fetal and maternal outcomes. A positive and significant correlation was found between nephritis history and preeclampsia as well as aPL antibodies and premature birth, and HTN and an increased rate of induced abortions. Both LN and anti-aPL antibodies exacerbated both maternal HTN and premature birth.[10]

Understanding the association between SLE and pregnancy is critical for healthcare providers in order to improve women's care and pregnancy outcomes.[7] The recommendations, therefore, are that pregnancies should be planned, SLE should be in remission for a minimum of six months and medications should be adjusted prior to pregnancy.[1]

Sultan Qaboos University Hospital (SQUH) is a tertiary hospital in Oman with multiple specialties, including a rheumatology unit and an obstetrics and gynaecology department with a maternal medicine team. The hospital receives patients from all over Oman, including far reaching areas, through the Emergency Department. Since pregnant women with SLE are mainly managed at two tertiary centres in Oman, the aim of this study was to share experiences in managing those patients at SQUH. This study was conducted by evaluating maternal and fetal outcomes and complications in pregnant women with SLE who were followed up and delivered at SQUH. This study aimed to determine risk factors that predict adverse outcomes for women with SLE and their babies.

Methods

A retrospective cohort study was conducted at SQUH from August 2006 to January 2016 and included 149 pregnancies in 98 women with SLE which met the American College of Rheumatology (ACR) 1997 classification criteria.[11] Delivery and neonatal ward registries were reviewed after obtaining ethical approval from the Ethics Committee of the College of Medicine and Health Sciences at Sultan Qaboos University (SQU). Pregnant women diagnosed with SLE who were in remission were included in the study. All patients were on prednisolone, hydroxychloroquine and aspirin as a standard of care. They were closely monitored during pregnancy with close follow-ups by maternal medicine specialists and rheumatologists who looked for symptoms and signs of lupus flare and adverse pregnancy outcomes. Patients with missing data, who delivered elsewhere, with disease activity just prior to pregnancy or who had been diagnosed with SLE during pregnancy were excluded from the study.

Collected maternal demographics included age, gravidity, parity, duration of disease, history of deep vein thrombosis (DVT), pulmonary embolism (PE), diabetes mellitus (DM), HTN, previous miscarriages, Caesarean section (CS) and intrauterine fetal death (IUFD).

Laboratory characteristics collected included anti-Sjögren syndrome-A (SSA)/anti-Ro, anti Sjögren syndrome-B (SSB)/anti-La, lupus anticoagulant (LAC), anti-cardiolipin antibody (aCL), anti-beta-2 glycoprotein 1 antibodies (anti-B2GP1), anti-double stranded deoxyribonucleic acid (anti-dsDNA), anti-nuclear antibody (ANA), C-reactive protein (CRP), complement 3 (C3), complement 4 (C4) and vitamin D3 levels.

Maternal outcomes reviewed included mode of delivery, gestational age at delivery and obstetrical complications. Complications included preeclampsia (i.e. gestational HTN with proteinuria), eclampsia (i.e. gestational HTN followed by one or more convulsions or coma as a consequence of convulsion), antepartum haemorrhage (APH) (i.e. prepartum bleeding starting from 22 gestational weeks) and postpartum haemorrhage (PPH) (i.e. 500–1000 mL or more of blood lost within 24 hours following delivery).[12–15] Disease manifestations reviewed included SLE flare, LN, the presence of antiphospholipid syndrome (APS), joint pain and involvement of other organs such as the heart. Fetal outcomes included miscarriage before 20 gestational weeks, IUFD or IUGR with an estimated fetal weight less than the tenth centile, birth weight, Apgar scores, admission to the neonatal intensive care unit (NICU), congenital heart block, prematurity and neonatal lupus.

Descriptive statistics were used to summarise data. Mean and standard deviation (SD) were used for continuous variables. For categorical variables, frequencies and percentages were reported. Continuous variables were analysed using Student's t-test where the distribution was normal. A Chi-squared test was used to evaluate the impact of clinical and laboratory characteristics on maternal and fetal outcomes. For cell frequencies ≤5, Fisher's exact test was used. Significant predictors of adverse pregnancy outcomes (i.e. miscarriage, CS, prematurity, IUFD, SLE flare, LN, joint pain, DVT, PE, preeclampsia, eclampsia, APH and PPH) were further analysed using multivariable logistic

Table 1: Maternal demographics of patients diagnosed with systemic lupus erythematosus who presented at Sultan Qaboos University Hospital from August 2006 to January 2016 (N = 149)

Variable	Number of pregnancies	Percentage	Range (Mean; SD)
Age	-	-	20–44 (30.6; 5)
Gravidity	-	-	1–12 (3.8; 2.4)
Parity	-	-	0–8 (2; 1.7)
History of miscarriages	50	33.56	-
History of DVT	19	12.75	-
History of PE	9	6.04	-
History of DM	51	34.46	-
History of HTN	18	12.16	-
History of CS	38	25.50	-
History of preeclampsia	8	5.41	-
History of eclampsia	2	1.35	-
History of IUFD	24	16.22	-
LN	18	12.08	-

SD = standard deviation; DVT = deep vein thrombosis; PE = pulmonary embolism; DM = diabetes mellitus; HTN = hypertension; CS = Caesarean section; IUFD = intrauterine fetal death; LN = lupus nephritis.

Table 2: Current pregnancy outcomes of patients diagnosed with systemic lupus erythematosus who presented at Sultan Qaboos University Hospital from August 2006 to January 2016 (N = 149)

Variable		Number of pregnancies	Percentage
Neonatal outomes	Live delivery	139	93.3
	Miscarriage	6	4.0
	IUFD	4	2.7
Mode of delivery	CS	47	33.8
	SVD	89	64
	Assisted	3	2.2
Preterm delivery (<37 weeks)		55	39.6
Eclampsia		3	2.0
Preeclampsia		11	7.4
APH		2	1.3
PPH		8	5.4
Joint pain		36	24.2
DVT		26	17.0
PE		11	7.4
Worsening LN		18	8.0

IUFD = intrauterine fetal death; CS = Caesarean section; SVD = spontaneous vaginal delivery; APH = antepartum haemorrhage; PPH = post-partum haemorrhage; DVT = deep vein thrombosis; PE = pulmonary embolism; LN = lupus nephritis.

regression and odds ratios (OR) with 95% confidence intervals (CI). Each pregnancy was considered a separate observation. In all cases, a *P*-value of <0.05 was considered statistically significant. All statistical analyses were performed using STATA, Version 13 (StataCorp, College Station, Texas, USA).

Results

In total, 149 pregnancies in 98 women with SLE were studied. Mean maternal age was 30.6 ± 5 years (range: 20–44), and the mean disease duration was 10 ± 5 years (range: 2–27). According to the SLEDAI index, all patients were in clinical remission. Previous pregnancy complications included miscarriages (n = 50; 33.56%), IUFD (n = 24; 16.22%), CS (n = 38; 25.50%), DVT (n = 19; 12.75%), PE (n = 9; 6.04%), preeclampsia (n = 8; 5.41%) and eclampsia (n = 2; 1.35%) [Table 1].

Clinical manifestations of SLE across the current pregnancies included arthritic joint pain (n = 36; 24.2%), LN (n = 18; 8%), preeclampsia (n = 11; 7.4%) and eclampsia (n = 3; 2%). APH and PPH were seen in two (1.3%) and eight (5.4%) pregnancies, respectively. Only one patient had lupus flare. This patient presented with joint pain at 23 gestational weeks and was managed with high-dose prednisolone. The patient was a 21-year-old primigravida with known SLE for two years. Her disease was in remission. Unfortunately, she experienced IUFD at 26 gestational weeks [Table 2].

Laboratory investigations were also considered. Positive ANA was found in 83 (56%) and positive anti-dsDNA antibodies in 80 (54%) pregnancies. CRP was elevated in 53 (36%) pregnancies. Anti-SSA and anti-SSB were positive in 68 (48.57%) and 15 (10.87%) pregnancies, respectively. In total, 25 patients (16.78%) had documented secondary APS prior to the current pregnancy. Positive anti-beta-2 glycoprotein1 antibodies were seen in 17 (11%) pregnancies as IgM antibodies while IgG was found in two (1.34%) pregnancies. Eight (5.37%) women were aCL IgG positive while nine (6.04%) pregnancies were aCL IgM positive. In addition, seven (4.70%) pregnancies had positive LAC. Furthermore, C3 and C4 were below the normal level in about 21 (14.09%) and seven (5%) pregnancies, respectively, but these patients were asymptomatic for lupus flare. Regarding

Table 3: Association of laboratory parameters and maternal lupus disease activity with adverse pregnancy outcomes (N = 149)

Clinical and Lab findings		Adverse pregnancy outcomes												
		MC	Fetal Loss	IUFD	PTB	CS	LN	Joint pain	APH	PPH	E	Pre-E	DVT	PE
HTN	Yes (n = 18)	3	3	0	12	9	5	1	0	3	0	5	4	0
	No (n = 130)	3	7	4	47	42	13	35	18	5	3	6	21	14
	P value	0.024	0.105	1.0	0.019	0.139	0.048	0.074	1.0	0.058	1.0	0.004	0.509	0.219
DM	Yes (n = 51)	4	5	1	16	18	9	9	1	3	0	2	14	8
	No (n = 97)	2	5	3	43	33	9	27	1	5	3	9	11	6
	P value	0.182	0.314	1.0	0.074	1.0	0.185	0.227	1.0	1.0	0.551	0.331	0.013	0.061
APS	Yes (n = 25)	3	4	1	16	10	2	6	0	4	0	1	8	5
	No (n = 124)	3	6	3	44	41	16	30	2	4	3	10	18	9
	P value	0.059	0.064	0.524	0.013	0.505	0.739	0.984	1.0	0.027	1.0	0.691	<0.001	<0.001
SSA/ Anti-Ro	Positive (n = 68)	1	2	1	33	18	7	18	0	4	3	7	9	3
	Negative (n = 72)	5	7	2	25	32	10	18	2	4	0	2	15	9
	Missing (n = 9)													
	P value	0.108	0.09	1.0	0.106	0.027	0.609	0.842	0.497	1.0	0.112	0.09	0.233	0.130
SSB/ Anti-La	Positive (n = 15)	0	0	0	7	2	1	6	0	1	0	0	1	2
	Negative (n = 123)	6	9	3	49	46	16	30	2	7	3	9	23	10
	Missing (n = 11)													
	P value	1.0	0.597	0.612	0.704	0.085	0.694	0.194	1.0	1.0	1.0	0.597	0.469	0.620
Low C3	Yes (n = 21)	0	0	0	11	13	3	9	0	1	2	5	2	1
	No (n = 122)	6	9	3	48	36	15	25	2	7	1	5	24	12
	Missing (n = 6)													
	P value	0.592	0.357	1.0	0.22	0.004	0.730	0.026	1.0	1.0	0.056	0.007	0.265	0.692
dsDNA	Positive (n = 80)	1	3	2	14	33	9	23	1	3	3	9	9	9
	Negative (n = 43)	4	4	0	36	7	5	7	1	4	0	1	7	3
	Missing (n = 26)													
	P value	0.05	0.238	0.542	0.156	0.005	1.0	0.125	1.0	0.238	0.551	0.163	0.429	0.539
LAC	Positive (n = 7)	1	2	1	1	4	0	0	0	1	0	0	2	1
	Negative (n = 126)	4	7	3	50	40	13	31	2	7	3	10	22	13
	Missing (n = 16)													
	P value	0.240	0.072	0.197	0.245	0.219	1.0	0.134	1.0	0.359	1.0	1.0	0.609	0.550
B2GP1	IgG Positive (n = 2)	0	0	0	1	0	0	1	0	1	0	0	1	0
	Negative (n = 106)	5	7	2	43	34	10	21	1	6	3	11	19	11
	Missing (n = 41)													
	P value	1.0	1.0	1.0	1.0	1.0	1.0	0.367	1.0	0.126	1.0	1.0	0.337	1.0
	IgM Positive (n = 17)	1	2	1	11	6	1	2	0	3	0	1	5	3

MC = miscarriage; IUFD = intrauterine fetal death; PTB = preterm birth; CS= Caesarean section; LN = lupus nephritis; APH = antepartum haemorrhage; PPH = postpartum haemorrhage; E = eclampsia; Pre-E = preeclampsia; DVT = deep vein thrombosis; PE = pulmonary embolism; HTN = hypertension; DM = diabetes mellitus; APS = antiphospholipid syndrome; SSA = Sjögren syndrome-A; SSB = Sjögren syndrome-B; C3 = complement 3; dsDNA = double stranded DNA; LAC = lupus anticoagulant; B2GP1 = beta-2 glycoprotein 1 antibodies; ACA = anti-cardiolipin antibody; IgG = immunoglobulin G; IgM = immunoglobulin M.

Table 3 (cont'd): Association of laboratory parameters and maternal lupus disease activity with adverse pregnancy outcomes

Clinical and Lab findings		Adverse pregnancy outcomes												
		MC	Fetal Loss	IUFD	PTB	CS	LN	Joint pain	APH	PPH	E	Pre-E	DVT	PE
B2GP1	Negative (n = 96)	4	5	1	34	33	11	21	1	4	3	10	15	8
	Missing (n = 33)													
	P value	0.565	0.283	0.279	0.03	0.941	0.690	0.517	1.0	0.068	1.0	1.0	0.179	0.367
ACA	IgG Positive (n = 8)	0	1	1	5	0	0	1	0	3	0	0	3	2
	Negative (n = 106)	5	7	2	40	37	10	26	1	4	3	9	18	11
	Missing (n = 35)													
	P value	1.0	0.452	0.198	0.266	0.052	1.0	0.678	1.0	0.007	1.0	1.0	0.163	0.226
	IgM Positive (n = 9)	0	1	1	7	4	0	1	0	2	0	1	2	2
	Negative (n = 111)	5	7	2	40	39	12	27	1	5	3	8	19	11
	Missing (n = 29)													
	P value	1.0	0.475	0.210	0.029	0.720	0.596	0.683	1.0	0.087	1.0	0.517	0.656	0.252
Vitamin D3	Deficient (n = 80)	3	4	1	33	22	5	22	1	5	2	8	15	7
	Sufficient (n = 52)	5	5	2	21	24	9	11	0	1	1	2	8	6
	Missing (n = 17)													
	P value	0.680	0.316	0.561	0.850	0.039	0.079	0.411	1.0	0.402	1.0	0.314	0.618	0.599

MC = miscarriage; IUFD = intrauterine fetal death; PTB = preterm birth; CS= Caesarean section; LN = lupus nephritis; APH = antepartum haemorrhage; PPH = postpartum haemorrhage; E = eclampsia; Pre-E = preeclampsia; DVT = deep vein thrombosis; PE = pulmonary embolism; HTN = hypertension; DM = diabetes mellitus; APS = antiphospholipid syndrome; SSA = Sjögren syndrome-A; SSB = Sjögren syndrome-B; C3 = complement 3; dsDNA = double stranded DNA; LAC = lupus anticoagulant; B2GP1 = beta-2 glycoprotein 1 antibodies; ACA = anti-cardiolipin antibody; IgG = immunoglobulin G; IgM = immunoglobulin M.

Vitamin D3 level, 80 (53.69%) women were deficient (Vitamin D [25-OH] <50 nmol/L) while 52 (34.9%) were insufficient (Vitamin D [25-OH] 50–75 nmol/L).

Out of 149 pregnancies, 139 (93.3%) were live births, six (4.02%) ended in a miscarriage and four (2.7%) were complicated by IUFD between 26–28 gestational weeks. Of the live births, 92 (66.1%) were vaginal deliveries and 47 (33.8%) were through CS mainly for obstetrical reasons, including previous CSs, severe preeclampsia or eclampsia. The mean gestational age at delivery was 36 ± 2 (range: 26–40) weeks. A total of 55 (39.6%) deliveries were preterm (i.e. <37 gestational weeks). Of those pregnancies, 35 (63.6%) occurred late preterm (i.e. >34 gestational weeks).

Out of the 92 vaginal deliveries, 89 (96.7%) were spontaneous while the other three (2.2%) were assisted vaginal deliveries via forceps or a vacuum device due to either non-reassuring fetal heart rate patterns on cardiotocogram or maternal exhaustion [Table 2].

The association between clinical and laboratory markers of disease in pregnant women with SLE and certain adverse pregnancy outcomes was analysed [Table 3]. Age was not a predictor for any of the adverse pregnancy outcomes. The association between preexisting HTN during the current pregnancy and several pregnancy outcomes was assessed. Significant associations were found between HTN and miscarriage ($P = 0.024$) and preterm birth ($P = 0.019$). In addition, HTN was positively associated with preeclampsia ($P = 0.004$) and LN ($P = 0.048$). DM was found to significantly affect the risk of DVT ($P = 0.013$) and increase PE risk, but this finding was not statistically significant ($P = 0.061$). Women who had three or more previous miscarriages had a higher risk of miscarriage in the current pregnancy (4/13 with recurrent miscarriage versus 2/129 without recurrent miscarriage) (OR = 19.8, 95% CI = 2.5–228.9; $P = 0.0016$).

APS impacted preterm birth ($P = 0.013$) and PPH ($P = 0.027$) and was found to be a significant predictor for developing DVT and PE ($P < 0.001$ for both). All patients with APS received low dose aspirin and prophylactic doses of low molecular weight heparin (Enoxaparin).

On studying the impact of Anti Sjögren's syndrome antibodies on adverse maternal outcomes, no clear influence was found for either anti-SSA or anti-SSB on any adverse pregnancy outcomes except

for an association between anti-SSA/anti-Ro and a lower risk of CS (P = 0.027).

The study showed a significant association between low C3 levels and preeclampsia (P = 0.007) and a trend towards an increased risk of eclampsia which was just below the level of significance (P = 0.056). In addition, low C3 levels were associated with increased risk of CS (P = 0.004) and joint pain (P = 0.026).

While studying the impact of high anti-dsDNA level on adverse maternal outcomes, a significant association with miscarriage (P = 0.05) and CS (P = 0.005) was reported. Positive LAC anti-B2GP1-IgG was not associated with adverse outcomes. On the contrary, anti-B2GP1-IgM was significantly associated with preterm birth (P = 0.03) and caused a higher risk of PPH, but the association was not statistically significant (P = 0.068). The only significant associations between adverse outcomes and aCL antibodies were between aCL-IgG and PPH (P = 0.007) and between aCL-IgM and pre-term birth (P = 0.029). Vitamin D levels did not influence pregnancy outcomes except for an unexpected association of higher Vitamin D levels (>50 nmol/L) with a higher risk of CS (P = 0.039).

Using multivariable regression of the main adverse outcomes of pregnancy, miscarriage was found to be significantly predicted by HTN (OR = 25.8, 95% CI = 2.8–231.3; P = 0.004) and dsDNA (OR = 0.07, 95% CI = 0.005–0.81; P = 0.034). Prematurity was determined by HTN (OR = 4.2, 95% CI = 1.2–14.9; P = 0.026), APS (OR = 3.8, 95% CI = 1.2–11.9; P = 0.022) and aCL-IgM (OR = 4.1, 95% CI = 0.8–26.7; P = 0.091) but not by anti-B2GP1-IgM (OR = 0.8, 95% CI = 0.2–3.4; P = 0.789). Multivariable analysis showed that CS risk was only influenced by positive anti-dsDNA (OR = 4.7, 95% CI = 1.4–15.4; P = 0.048) and higher vitamin D levels (OR = 2.8, 95% CI = 1.2–6.8; P = 0.02). PPH had a significant association only with aCL-IgG (OR = 10.7, 95% CI = 1.7–67.6; P = 0.012). Preeclampsia was almost equally determined by both HTN and low C3, with ORs of 14.4 and 15.3, respectively (95% CI = 2.4–86.3 and 2.8–85.2, respectively) and P-values of 0.003 and 0.002, respectively. DVT was found to correlate with DM (OR = 8.9, 95% CI = 1.9–42.8; P = 0.006) and APS (OR = 87.2, 95% CI = 17.8–427.7; P <0.001).

As discussed above, prematurity was seen in 50 babies, and four suffered an IUFD. Mean birth weight in the study sample was 2.72 ± 0.673 kg; range: 0.525–4.25 kg). IUGR was observed in 49 babies (35%) mainly due to preterm birth (n = 34). In total, 11 newborns had an Apgar score of less than seven at one minute, and only three had a score of less than seven at five minutes. About one-third of the neonates (n = 45; 33%) were admitted to the neonatal intensive care unit (NICU) due to respiratory distress, neonatal sepsis or prematurity and one neonate suffered from intraventricular haemorrhage. No neonatal lupus or congenital heart block was seen in the study sample.

APS significantly predicted prematurity (P = 0.013). Fetal loss was also found to be higher in patients with APS and among those who were LAC positive, but the associations did not reach statistical significance (P = 0.064 and 0.072, respectively).

Discussion

This study looked into various pregnancy outcomes and predictors that resulted in complications. In this study, most pregnancies (93.3%) resulted in live births. The incidence of live births in pregnancies complicated by SLE was reported as ranging from 72–89% in larger studies done in Argentina and North America.[16,17] In contrast, an Egyptian study reported a much lower incidence (45–50%).[9] The higher live birth rate in this study could be attributed to good disease control but could also be due to the fact that the current patients were in clinical remission before conception except for one case who was in flare during pregnancy, and that case resulted in IUFD. Most pregnancies ended with a normal vaginal delivery (64%), while 33.8% were delivered by CS and 4% resulted in miscarriage. Preterm delivery occurred in 39.6% of the pregnancies and mostly in late preterm after 34 gestational weeks. In a previous prospective study in California that included 91 SLE pregnancies, a higher rate of CS deliveries (53%) was seen, while only 32% had a normal vaginal delivery.[9] A similar rate of preterm birth was reported in previous studies, with the rate reaching up to 54%.[7,9,18] The current results showed six cases of miscarriage (4%). A miscarriage incidence of 11–24% was reported in SLE pregnancies in a prospective study in France.[19] On the other hand, a range of fetal loss rates were reported in rheumatic disease clinics in North America, with cases occurring in 10% of mild LN cases and in up to 60% of severe cases.[16,20] In contrast, this study found four (2.7%) women with fetal loss and only one of the women had LN. In general, the fetal loss rate is comparable to healthy women (8–12%) for women with inactive SLE at conception.[21]

Despite improvements in pregnancy management in patients with SLE, adverse pregnancy outcomes and higher perinatal morbidity and mortality risk are still noticed in comparison with pregnant women without SLE, even among those who are in clinical remission.[16,18,22] In this retrospective cohort study, preeclampsia was observed in 7.4% of the patients while ranges from 3–26% were reported in similar studies in Argentina.[19] Nevertheless, only 2% of the current patients progressed to eclampsia. The current

study reported 12.08% of patients with LN during pregnancy while another similar study reported higher rates (21%).[9] This variation might be explained by good disease and HTN control in the current patient cohort.

Autoantibodies and ANA serve as key diagnostic and classification criteria for SLE, with the latter being recently used as entry criteria for diagnosing SLE.[23,24] ANA was detected in only 56% of the current cohort, which is lower than expected. This finding could be explained by low numbers in the cases studied, variability in testing protocols, type of assay used or not repeating the testing. A recent study concluded that ANA is not always found in SLE patients.[25] The researchers reported negative and fluctuating ANA results in 36.9% and 33.3% of patients, respectively. Another study found ANA positivity in only 23.7% of patients.[26]

This study examined various predictors that resulted in adverse pregnancy outcomes. A significant association was found between HTN and miscarriage, preterm birth, pre-eclampsia and LN. Similarly, a study done at the University of California Davis School of Medicine reported a significant association between HTN and miscarriage as well as preterm birth ($P = 0.001$ and 0.017, respectively).[8] An increased risk of developing preeclampsia and LN was also found in previous studies.[9,27]

APS is frequently seen in patients with SLE and may result in various pregnancy-related complications. APS was found in 16.78% of the pregnancies in the current cohort. Similarly, a meta-analysis reported its presence in approximately one-quarter of the pregnancies in which the mother had been diagnosed with lupus.[10] The presence of APS is strongly associated with the development of DVT, PE and fetal loss but, in the current study, the latter did not reach statistical significance. Previous studies have reported similar outcomes.[5,9,28] An Italian study correlated APS with prematurity and this correlation was also observed in the current study.[1] In addition, APS was associated with PPH in the current cohort which could be attributed to antithrombotic treatment; such a correlation, however, was not reported in previous studies.[29,30]

A study conducted in Mexico of 1,334 pregnant women with SLE reported low C3 levels in almost 50% of the patients.[31] This finding is considered a very high incidence in comparison with the current finding as only 14.09% of the current cohort had low C3 levels. Patients with low C3 levels were more likely to deliver via CS, but this observation could be related to obstetrical indications. More research is needed in order to establish the possibility of a causal relationship.

Preeclampsia in the current study was exacerbated by low C3 level. Patients with low C3 level were 15 times more likely to develop preeclampsia than those with normal C3 levels (OR = 15.3). In contrast, other studies have shown positive associations between preexisting renal disease and HTN.[7] This finding was not present in the current study probably because of a limited sample size. In comparison, eclampsia was only present with a decreased level of C3 ($P = 0.035$).

The presence of anti Ro/SSA and anti La/SSB antibodies has been associated with neonatal lupus and congenital heart block (CHB) in previous studies.[32,33] None of the current neonates, however, had neonatal lupus or CHB, perhaps due to the finding that maternal antibodies were low in this cohort. In addition, the current patients were on hydroxychloroquine, which is usually associated with a lower risk of CHB.[34,35]

This study successfully detected factors that can be used as indicators to determine women with SLE who might be at risk of adverse pregnancy outcomes. A significant relationship was found between HTN and preterm birth, preeclampsia, LN and miscarriage. These findings along with those of other practitioners can be used to establish guidelines to help doctors treat and manage pregnant women with SLE, thus resulting in successful outcomes.

This study has multiple limitations including a small sample size which is due to the small population in Oman compared to other countries and the fact that it was conducted in a single tertiary centre. However, the study was sufficiently powered (85%) to detect a rate of preeclampsia of up to 22.5% and predict the effect of HTN on preeclampsia. In total, 45% of hypertensive women in the current study developed preeclampsia. A significant drawback was that this study did not look at SLE pharmacological management and its relation to various pregnancy outcomes. Finally, a comparative study with healthy pregnant women is recommended to solidify knowledge and guideline development.

Conclusion

Although most pregnancies complicated by SLE have good outcomes, adverse outcomes may still occur in women with SLE. Planning pregnancies and careful pregnancy monitoring coupled with efficient treatment need to be enhanced for successful outcomes. Further studies which include larger sample sizes and multiple centres caring for women with SLE are recommended.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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