Neonatal and Obstetrical Outcomes of Pregnancies in Systemic Lupus Erythematosus

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ABSTRACT

Objectives: Systemic lupus erythematous (SLE) is a chronic autoimmune disease that affects women primarily of childbearing age. The objective of this study was to determine the neonatal and maternal outcomes of pregnancies in SLE patients compared to pregnancies in healthy controls. *Methods:* We conducted a retrospective cohort study in a tertiary care hospital in Oman between January 2007 and December 2013. We analyzed 147 pregnancies and compared 56 (38.0%) pregnancies in women with SLE with 91 (61.9%) pregnancies in healthy control women. Disease activity was determined using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). *Results:* The mean age of the cohort was 30.0±5.0 years ranging from 19 to 44 years old. Patients with SLE were treated with hydroxychloroquine (n = 41; 73.2%), prednisolone (n = 38; 67.8%), and azathioprine (n = 17; 30.3%). There was no disease activity in 39.2% (n = 22) of patients while 41.0% (n = 23), 12.5% (n = 7), and 7.1% (n = 4) had mild (SLEDAI 1–5), moderate (SLEDAI 6–10), and severe (SLEDAI ≥ 11) disease activity, respectively, at onset of pregnancy. Pregnancies in patients with SLE were associated with higher abortions (42.8% vs. 15.3%; $p < 0.001$), gestational diabetes (28.3% vs. 10.2%; $p = 0.004$), polyhydramnios (7.1% vs. 0.0%; $p = 0.020$), previous preterm pregnancies (8.9% vs. 1.0%; $p = 0.030$), and intrauterine growth retardation (21.4% vs. 0.0%; $p < 0.001$) when compared to pregnancies in healthy control women. Furthermore, the neonates born to mothers with SLE were more likely to be preterm (28.5% vs. 1.0%; $p < 0.001$), have a low birth weight (< 2 500 g) (32.1% vs. 1.0%; $p < 0.001$), and were associated with stillbirth (7.1% vs. 0.0%; $p = 0.010$) when compared to neonates born to healthy control mothers. *Conclusions:* Pregnancies in women with SLE were associated with higher neonatal and maternal complications. Therefore, pregnant women with SLE should have their pregnancy accurately planned, monitored, and managed according to a multidisciplinary treatment schedule.

Systemic lupus erythematosus (SLE) is an autoimmune disease with a diverse clinical phenotype characterized by the presence of autoreactive B and T cells, which are responsible for the aberrant production of a heterogeneous group of autoantibodies. Neonatal SLE (NSLE) occurs as a result of the transplacental passage of maternal immunoglobulin G (IgG) autoantibodies against Sjögren's syndrome A-B (SSA (Ro) and SSB (La)), and/or U1 ribonucleoprotein (U1-RNP). However, only 1–2% of infants with positive maternal autoantibodies develop NSLE.[1] Besides SLE, mothers of neonates with NSLE may have other defined or undifferentiated autoimmune disorders, such as Sjögren's syndrome, undifferentiated autoimmune syndrome, or rheumatoid arthritis.[1] The major clinical manifestations of NSLE include neonatal heart block and subacute cutaneous lupus lesions. Hepatobiliary and hematological cytopenias are also well established, although less common. Rarely, urinary abnormalities and neurological involvement have been reported.[1]

There seem to be conflicting results on the impact of pregnancy on disease activity in patients with SLE. While some studies show no change in activity, and various other studies have demonstrated an increase in lupus activity during pregnancy.[2–4] Furthermore, specific maternal factors in patients

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with SLE during pregnancy, such as active disease, lupus nephritis and specific antibodies such as antiphospholipid, anti-Ro/SSA, and anti-La/SSB are found to be associated with unfavorable neonatal outcomes.[5] However, other prospective studies have not indicated such relationships.[6–8] The differences may be explained by the diversity of presentation, limited number of patients included in the various studies, lack of standardized criteria for defining lupus flares, and different treatments used in the management of SLE during pregnancy.[9] In addition, several manifestations secondary to pregnancy may be erroneously attributed to lupus flares, including arthralgia, myalgia, facial rash, and edema in the face, hands, and lower limbs. Equally, serological abnormalities used to define lupus flares may be physiologically altered during pregnancy, such as complement levels and inflammatory markers.[8]

Although many studies have been forthcoming from Euro-American populations, there are some indications in the existing literature that race and ethnicities may impact disease susceptibility and manifestations.[10–12] More severe disease occurs in African Americans and Asians resulting in increased morbidity and higher mortality rates in these groups.[13] There are limited studies in SLE patients emanating from the Arab world; however, it is recognized that Arabs experience a different disease burden than those from Europe and North America with a higher burden of disease and different frequency of disease manifestation.[14,15]

The objective of this study was to describe the neonatal and obstetrical outcomes of pregnancies in SLE patients compared to healthy pregnant controls in an Arab cohort population from Oman.

METHODS

This retrospective study was conducted at Sultan Qaboos University Hospital, one of the rheumatology referral centers in Oman. The patients treated in the clinics are referred from all governorates in the country and are representative of the population as a whole. The study population included consecutive neonates born to mothers with SLE from January 2007 to December 2013. The control group included consecutive neonates born to healthy mothers during the same study period. The data collected from neonates of both cohort groups included demographic data such as gestational age,

gender, birth weight, growth restriction, and Apgar scores.[16] Gestational age was considered preterm if neonate was born < 37 weeks of gestation and term if the neonate was born ≥ 37 weeks gestation. Low birth weight (LBW) was defined as infants < 2 500 g and intrauterine growth retardation (IUGR) was defined as fetal weight < 10th percentile for gestational age. Apgar scores < 7 at one minute were considered abnormal. The data collected from neonates born to mothers with SLE included clinical manifestations of NSLE including skin, cardiac, hematological, and liver involvement in addition to duration and circulating maternal autoantibody profile.

All mothers with a diagnosis of SLE were > 18 years old and fulfilled the American College of Rheumatology (ACR) 1997 revised criteria for the classification of SLE.[17] The control group was made up of age- and parity-matched healthy mothers. The data collected from both cohorts of mothers included obstetrical complications during pregnancy such as the occurrence of gestational diabetes, pre-eclampsia, oligohydramnios or polyhydramnios. Information on previous obstetric complications (i.e., previous abortion, preterm labor, intrauterine fetal death (IUFD) or stillbirth) were also collected. Gestational diabetes was defined as glucose intolerance of variable degree with onset or first recognition during pregnancy, and pre-eclampsia was defined as hypertension and proteinuria with or without pathological edema. Polyhydramnios and oligohydramnios were diagnosed when the amniotic fluid index was < 24 cm and < 5 cm, respectively.

The data collected from mothers with SLE included demographics, clinical features of SLE since onset of diagnosis, disease activity at onset of pregnancy, and disease flares during pregnancy. Other data collected included immunological parameters at onset of pregnancy and medications used during pregnancy. The main SLE clinical manifestations evaluated in this study were defined according to the American Rheumatism Association glossary committee. The immunological parameters recorded included antinuclear antibody (ANA) determined by immunofluorescence using Hep-2 cells as substrate. Anti-double stranded DNA antibody (anti-dsDNA), extractable nuclear antigen, and antiphospholipid antibodies (APLA) were measured qualitatively using enzyme-linked immunosorbent assay technique (ELISA). The results were expressed

in international units. Complement C3 and C4 levels were measured by nephelometry. In addition, SLE disease activity at the onset of pregnancy and disease flares during pregnancy were measured using the SLE Disease Activity Index (SLEDAI) score. SLEDAI is a validated and reliable measuring tool.[18] Disease activity categories were defined on the basis of SLEDAI scores: no activity (SLEDAI = 0), mild activity (SLEDAI = 1–5), moderate activity (SLEDAI = 6–10), high activity (SLEDAI = 11–19), and very high activity (SLEDAI ≥ 20).[14] A disease flare of SLE is defined as an increase in SLEDAI of > 3, and a SLEDAI score of > 5 is associated with a probability of initiating or changing therapy in more than 50% of instances.[19]

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's chi-square tests (or Fisher's exact tests for cells < 5). For continuous variables, mean and standard deviation (SD) were used to summarize the data. Analyses were performed using Student's t-tests. A priori two-tailed level of significance was set at 0.05. Statistical analyses were conducted using STATA version 13.1 (STATA Corporation, College Station, TX, USA).

Ethical approval was obtained from the Ethics Committee of the College of Medicine and Health Sciences, Muscat, Oman; Sultan Qaboos University; MREC #873 dated 2 April 2014.

RESULTS

A total of 147 infants were compared during the study period, 56 (38.0%) infants were born to

Table 1: Neonatal outcomes of infants born to mothers with SLE compared to those born to healthy control mothers. Data presented as n (%) unless otherwise stated.

Characteristics	All (n = 147)	Control (n = 91)	SLE (n = 56)	p-value
Gender, n (m/f) ratio	53.0/47.0 (1:1.12)	54.0/46.0 (1:1.17)	52.0/48.0 (1:1.08)	0.808
Birth weight, mean ± SD, kg	2.8 ± 0.4	3.0 ± 0.2	2.6 ± 0.6	< 0.001
LBW	19 (12.9)	1 (1.0)	18 (32.1)	< 0.001
IUGR	12 (8.1)	0 (0.0)	12 (21.4)	< 0.001
Gestational age				
Preterm (> 37 weeks)	17 (11.5)	1 (1.0)	16 (28.5)	< 0.001
Term (≥ 37 weeks)	130 (88.4)	90 (98.9)	40 (71.4)	
Apgar score at 1 minute < 7	2 (1.3)	0 (0.0)	2 (3.5)	0.069

SLE: systemic lupus erythematosus; SD: standard deviation; LBW: low birth weight (< 2.5 kg); IUGR: intrauterine growth retardation.
Percentages may not add up to 100% due to rounding off.

Table 2: Obstetrical outcomes of mothers with SLE compared to healthy control mothers. Data presented as n (%) unless otherwise stated.

Characteristics	All (n = 147)	Non-SLE (n = 91)	SLE (n = 56)	p-value
Age, mean ± SD, years	30.0 ± 5.0	29.0 ± 5.0	31.0 ± 5.0	0.145
Prior pregnancies				0.084
Primigravida (1)	35 (23.8)	24 (26.3)	11 (19.6)	
Multigravida (2–4)	79 (53.7)	52 (57.1)	27 (48.2)	
Grand multigravida (> 5)	33 (22.4)	15 (16.4)	18 (32.1)	
Obstetrical outcomes				
Gestational diabetes*	24 (16.6)	9 (10.2)	15 (28.3)	0.004
Pre-eclampsia	5 (3.4)	2 (2.1)	3 (5.3)	0.369
Oligohydramnios	1 (0.6)	0 (0.0)	1 (1.7)	0.381
Polyhydramnios	4 (2.7)	0 (0.0)	4 (7.1)	0.020
Previous outcomes				
Abortions	38 (25.8)	14 (15.3)	24 (42.8)	< 0.001
Preterm labor	6 (4.0)	1 (1.0)	5 (8.9)	0.030
Still birth/IUFD	4 (2.7)	0 (0.0)	4 (7.1)	0.010

SLE: systemic lupus erythematosus; SD: standard deviation; IUFD: intrauterine fetal death.
*Gestational diabetes details were missing for three mothers.
Percentages may not add up to 100% due to rounding off.

Table 3: Clinical features of mothers with SLE.

Characteristics	SLE (n = 56)	Percentage
Clinical manifestations		
Musculoskeletal	27	48.2
Cutaneous	21	37.5
Hematology	14	25.0
Thrombocytopenia	6	10.7
Hemolytic anemia	8	14.2
Lymphadenopathy	1	1.7
Lung	4	7.1
Central nervous system	6	10.7
Constitutional symptoms	5	8.9
Lupus nephritis	10	17.8
Autoantibody profile		
Antinuclear antibodies	53	94.6
dsDNA	29	51.7
SSA	20	35.7
SSB	8	14.2
Anti-Ro2	9	16.0
Ribonucleoprotein	10	17.8
Histone	13	23.2
Sm	7	12.5
Nucleosome	1	1.7
Ribosome	1	1.7
Antiphospholipid antibodies	14	25.0
Lupus anticoagulant	1	1.7
Cardiolipin	6	10.7
B2 glycoprotein	11	19.6
Others		
Gastric parietal cell	1	1.7
Tissue transglutaminase	1	1.7
Thyroid	1	1.7
Medications		
Hydroxychloroquine	41	73.2
Azathioprine	17	30.3
Prednisolone, mg	38	67.8
< 5	0	0.0
5–10	32	57.1
> 10	6	10.7
SLEDAI		
0 (no activity)	22	39.2
1–5 (mild)	23	41.0
6–10 (moderate)	7	12.5
≥ 11 (severe)	4	7.1
Disease flares	16	28.5

SLE: systemic lupus erythematosus; dsDNA: double standard DNA; SSA: Sjögren's syndrome A; SSB: Sjögren's syndrome B; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.
Percentages may not add up to 100% due to rounding off.

mothers with SLE while 91 (61.9%) infants were born to healthy control mothers [Table 1]. Among the newborn infants, the male to female ratio was similar in distribution with no significant differences between the two study cohorts (1.17% vs. 1.08%; $p = 0.808$). However, infants born to mothers with SLE compared to normal healthy controls had a lower mean birth weight (2.6 vs. 3.0 kg; $p < 0.001$), a higher incidence of LBW (32.1% vs. 1.0%; risk ratio (RR) 29.20; 95% confidence interval (CI): 5.24–71.5; $p < 0.001$) and higher incidence of IUGR (21.4% vs. 0.0%; $p < 0.001$). In addition, there was also a higher incidence of preterm birth (28.5% vs. 1.0%; RR 26.00; 95% CI: 4.44–68.9; $p < 0.001$).

The clinical manifestation of infants born to mothers with SLE displayed increases in transaminases (n = 14; 25.0%), mild cytopenias (n = 6; 10.7%), and cutaneous involvement (n = 2; 3.5%). All affected neonates had spontaneous resolution of clinical involvement within 3–6 months follow-up. The mean duration of circulating maternal antibody profile in neonates was 6.6±2.9 months with a range of 2–15 months (not shown in tables). Despite the fact that anti-Ro2 antibody was present in 21.4% (n = 12) of infants born to mothers with SLE, none of the neonates developed congenital heart block.

The maternal age and obstetrical outcomes of 147 pregnancies are described in Table 2. There were no significant differences in the mean age ($p = 0.145$) or maternal parity ($p = 0.084$) between the groups. The pregnancies in mothers with SLE were associated with higher complications including gestational diabetes (28.3% vs. 10.2%; RR 2.86; 95% CI: 1.38–5.01; $p = 0.004$) and polyhydramnios (7.1% vs. 0%; $p = 0.020$). The patients with SLE were also more likely to have a history of previous obstetrical complications including previous abortions (42.8% vs. 15.3%; RR 2.79; 95% CI: 1.67–4.03; $p < 0.001$), previous preterm labor (8.9% vs. 1.0%; RR 8.13; 95% CI: 1.01–42.1; $p < 0.001$) and previous IUFD/stillbirth (7.1% vs. 0% $p = 0.010$).

The clinical manifestations of mothers with SLE are described in Table 3. The most common clinical features were musculoskeletal (n = 27; 48.2%) and cutaneous (n = 21; 37.5%) followed by hematological complications (n = 14; 25.0%). The most common autoantibody profile include positive ANA (n = 53; 94.6%) followed by dsDNA (n = 29; 51.7%) and anti-SSA antibody (n = 20; 35.7%). The

treatment mostly consisted of hydroxychloroquine (HCQ) (n = 41; 73.2%), prednisolone (n = 38; 67.8%), and azathioprine (30.3%). Despite a high percentage of mothers with SLE being on steroids during pregnancy, the majority were on low dose prednisolone 5–10 mg (n = 32; 57.1%). Up to 80.2% (n = 45) of mothers with SLE were in clinical remission or with mild disease activity at onset of pregnancy and only 28.5% (n = 16) had disease flare during pregnancy.

DISCUSSION

Our study revealed poor neonatal outcomes in mothers with SLE, namely, preterm birth, IUGR, and LBW infants. Our cohort also had a history of poor obstetrical outcomes including previous abortions, previous preterm births, and previous IUFD or stillbirth. Our findings are comparable to other studies which have demonstrated that the main neonatal morbidities in patients with SLE include increased rate of fetal loss, preterm births, IUGR, and neonatal lupus syndrome.[20,21] Similarly, other studies have demonstrated that pregnancies of women with SLE are complicated by fetal growth restriction and small for gestational age babies in 10–30% of cases.[22]

In our cohort, the clinical manifestations of infants born with NSLE were hepatobiliary (25.0%), cytopenia (11.0%), and cutaneous (3.8%), which is different to what is commonly described in the literature with the occurrence of cutaneous, cardiac, hepatobiliary, and hematologic manifestation in 70%, 65%, 53%, and 45%, respectively.[23] In our cohort of multigravida mothers with SLE, 44.6% (n = 25) had positive antibodies (SSA and SSB). Of these, NSLE occurred in 48.0% (n = 12), greater than described in the literature. Typically, 1–2% of seropositive mothers (SSA and SSB) will give birth to an infant with NSLE.[1] In those who had an infant with NSLE, the risk increases to 25% in future pregnancies. It is interesting to note that NSLE occurred in 25.0% (n = 14) of infants with other antibodies namely dsDNA and RNP.

Pre-eclampsia, active disease, lupus nephritis, thrombocytopenia, and presence of APLA have been reported to be associated with poor outcomes in SLE pregnancies.[24–28] In our cohort, these risk factors occurred in relatively low frequency. The patients had moderate to severe disease activity

in 19.6% of the cohort while 28.5% experienced disease flare during pregnancy. There was also a relatively low incidence of lupus nephritis (17.8%), thrombocytopenia (10.7%), and pre-eclampsia (5.3%). However, there was a relatively high incidence of antiphospholipid antibody (25.0%; n = 14), which may have contributed to increased risk of neonatal outcomes. However, we were unable to statistically evaluate if this was a true risk factor due to the small sample size of our cohort.

Pregnancies in mothers with SLE tend to adversely affect maternal outcomes. A large national data base study in the US, which included 16.7 million deliveries, reported an increased risk of maternal death, pre-eclampsia, preterm labor, thrombosis, and infectious complications during pregnancy.[21] Of the estimated annual 4 500 pregnancies in women with SLE each year in the US, up to one-third of the deliveries are the result of cesarean sections.[5] However, in our cohort, apart from preterm labor, these complications were not observed most likely due to the high remission rate and low disease activity (80.2%) at pregnancy onset and close follow-up in a high-risk obstetric clinic.

Steroid exposure should be restricted to a minimum during pregnancy.[21] Higher doses of steroids during pregnancy are associated with an increased risk of diabetes, hypertension, pre-eclampsia, and premature rupture of membranes.[29] In our patient cohort, 67.8% were on oral prednisolone during pregnancy, however, up to 57.1% of those patients were on a low dose (5–10 mg). This could have contributed to the higher rate of gestational diabetes in our cohort of mothers with SLE compared to healthy controls. However, we did not encounter other associated risks of steroids in our patients.

HCQ should be continued throughout pregnancy in mothers with SLE. Multiple studies have demonstrated advantageous effects of HCQ use during pregnancy in mothers with SLE such as reduction in disease activity, while discontinuation led to flares in disease activity.[30,31] The sustained use of HCQ has also demonstrated a reduced risk of congenital heart block and neonatal lupus syndromes with no adverse effects on the infants.[32,33] However, despite these recommendations, only 73.2% of our patients were compliant. Perhaps improvement in neonatal outcomes in the future can be observed with increasing adherence to HCQ. Azathioprine

is one of the few immunosuppressive agents that has documented safety during pregnancy and was used in 30.3% of patients in our cohort.[29] An association between maternal azathioprine therapy during pregnancy and the occurrence of developmental delay in offspring has been suggested.[34] Aspirin and low molecular weight heparin were administered to all patients with circulating APLA in our cohort. Low molecular weight heparin was transitioned to unfractionated heparin before delivery. Perhaps the judicious use of these anticoagulants resulted in a decreased occurrence of thrombosis in our cohort despite the relatively high rate (25.0%) of circulating APLA.

The influence of race and ethnicity on pregnancy outcome in SLE patients has been described.[35,36] African American and Hispanic women with lupus have a higher rate of obstetric complications including chronic hypertension, renal failure, pneumonia, cesarean delivery, preterm labor, eclampsia, and fetal growth restriction compared with white women.[35,36] Although adverse outcomes were more frequent in African Americans and Hispanics; multivariable analyses indicated that it was education rather than ethnicity that was independently associated with adverse pregnancy outcomes.[37] There are limited studies on pregnancy outcomes in patients with SLE of Arab ethnicity. However, in a study of 319 women with lupus from Saudia Arabia, 176 (55%) women conceived resulting in 396 pregnancies and 269 live births. The frequency of fetal loss and preterm birth were 22% and 27%, respectively.[38] Fetal loss was significantly higher in patients with APLA, lupus nephritis, anti-Ro antibody, hypertension, and a history of intravenous cyclophosphamide. SLE flares occurred in 30.8% of pregnancies and were associated with increased risk of fetal loss, preterm births, and IUGR.[39] In another study in the region, there were no differences in the frequency of lupus manifestations between Arab and Jewish patients with SLE in northern Israel.[40] An adverse pregnancy outcome occurred in 35.6% of pregnancies. APLA positivity, past major organ involvement, and a younger age at conception were associated with adverse pregnancy outcomes.[40] Based on these limited studies, with the addition of the results from our study, it seems that obstetrical outcomes of mothers with SLE in Arab patients are similar to European and North American cohorts.

One of the limitations of the study is its retrospective nature. Additionally, a few of the mothers with SLE, who were followed in our clinics, delivered at their local hospitals due to geographical proximity. Perhaps these patients had a milder disease course and neonatal outcomes. This might indirectly affect the results of the study as these patients were not included in our analysis. Nevertheless, it appears that during pregnancy SLE remains a disease associated with significant neonatal morbidity and obstetrical complications. However, with better control of disease activity, pregnancy in SLE patients is no longer an absolute contraindication. Careful planning of pregnancy coupled with multidisciplinary monitoring with early detection of threats with judicious use of appropriate treatment is the key to achieve good outcomes.

CONCLUSION

Our population-based study demonstrates worse neonatal and obstetrical outcomes for women with SLE than the general population. In addition to preterm labor, IUGR, and LBW, pregnant mothers with SLE are more likely to also have gestational diabetes and polyhydramnios. This information will assist in maternal counseling of perinatal prognosis, highlighting the importance of cautious multidisciplinary care throughout pregnancy to improve both maternal and fetal outcomes.

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