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Obstetrics outcome in women with Systemic Lupus Erythematosus

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Abstract

Introduction: For many years pregnancy has been contraindicated in patients with Systemic Lupus Erythematosus, particularly when kidney involvement was present. Today, pregnancy is no longer considered impossible in woman with lupus. Yet lupus pregnancies are still considered high- risk. The prognosis has considerably improved for pregnant woman but the foetal risk, although progressively reduced, is still higher in pregnancies of patient with systemic lupus erythematosus than in pregnancies of healthy woman. Miscarriage, premature delivery, and preeclampsia are common complications whereas heart problems can occur in the babies.

In this paper we reviewed the obstetric outcome with pregnant woman with systemic lupus erythematosus, the influence of lupus on fetal outcome, the effects of pregnancy on lupus, and the management of pregnant lupus patients based on our personal experience.

Material and methods: We performed a retrospective study of pregnancy outcomes in antenatal woman with systemic lupus erythematosus in our institute from January 2020 to July 2021. A total of 13 woman with systemic lupus erythematosus were analysed. In included age, obstetrics co-morbidities, diagnostic test for systemic lupus erythematosus, systemic involvement, management and obstetrics and perinatal complications also.

Results: The mean age of antenatal woman with systemic lupus erythematosus was 27.2 years. The rate of active disease at conception, antiphospholipid syndrome and lupus nephritis were 15.38%,30.7% and 69.23% respectively. systemic lupus erythematosus flare occurred in 3 out of 13 pregnancies. Whereas 7 pregnancies complicated with preeclampsia. The live

birth rate in our study was 61.53%. on univariate analysis, active disease and flare in pregnancy were both strongly associated with fetal loss. Systemic lupus erythematosus flare and antiphospholipid syndrome increased the risk of pre-eclampsia. Aspirin, HCQ and prednisolone were protective against the fetal loss.

Conclusion: Aspirin should be used in all systemic lupus erythematosus patients to reduce risk of foetal loss. HCQ and prednisolone seem to have a protective effect against pre-eclampsia and should be considered in all the women planning pregnancy.

Introduction

Systemic lupus erythematous (systemic lupus erythematosus) is a chronic inflammatory disease with multisystem involvement in which the tissues are damaged by autoantibodies and immune complexes and primarily affects young female at childbearing age {1}. Pregnancy is of importance in every woman's life. However, different maternal diseases can complicate pregnancy. One of them is systemic lupus erythematosus, which can turn the life miserable during pregnancy, if it is not treated properly {2}.

Pregnancy in woman with systemic lupus erythematosus carries a higher maternal and fetal risk compared with pregnancy in healthy woman. The prognosis for both mother and child are best when systemic lupus erythematosus has been quiescent for at least six months prior to the pregnancy. Disease flares during systemic lupus erythematosus pregnancy pose challenges with respect to distinguishing physiologic changes related to pregnancy from disease related manifestations. Thus, a multidisciplinary approach with close medical, obstetric, and neonatal monitoring is necessary to optimize both maternal and fetal outcomes {3}.

Pregnancy in systemic lupus erythematosus woman carry higher maternal and fetal risks when compared with general populations. Maternal complications include flare, worsening of renal function, preeclampsia and thrombotic events, while fetal risk involve miscarriage, intrauterine growth retardation, premature delivery and neonatal lupus syndrome {4}.

To improve pregnancy outcome, woman is advised to avoid pregnancy during active disease and after at least 6 month of disease remission {5}. Remission of disease prior to conception is associated with reduced rate of pregnancy loss, preterm birth, pregnancy induced hypertension and fetal growth restriction {6}. Active disease at conception, lupus nephritis, chronic hypertension and antiphospholipid syndrome are common risk factors associated with poor pregnancy outcomes {7,8,9}.

Material and methods

This retrospective study conducted at N. K. P. Salve Institute of Medical Science and Research Centre, Nagpur. All pregnant woman who was diagnosed with systemic lupus erythematosus as per the American College of Rheumatology classification criteria {10} and completed their pregnancy from January 2020 to July 2021 were included in this study.

Patients medical record including obstetrics notes, operation reports, outpatient medical records and hospital discharge summaries were reviewed. Demographic data, systemic lupus erythematosus clinical manifestation and treatment, duration of systemic lupus erythematosus diagnosis and remission, the presence of systemic lupus erythematosus flare, treatment during pregnancy and pregnancy outcome were recorded. The systemic lupus erythematosus Disease activity Index (SLEDAI) was used to access

disease activity whereas SLEDAI less than 4 considered in remission whereas 4 and above was considered active disease {11}. Laboratory investigations including serum creatinine, antinuclear antibodies (ANA), anti-double stranded DNA antibodies (anti- ds DNA), lupus anticoagulant, anticardiolipin antibody (Acl), complement 3 (C3), complement 4 (C4) and proteinuria were recorded. Anti–RO and Anti–La antibodies were recorded if available.

Pregnancy outcome recorded included live birth including term and preterm, miscarriage, stillbirths and mode of delivery. Fetal loss was defined as the total number of miscarriage and stillbirths {12,13}.

Maternal outcome assessed were preeclampsia, eclampsia, and flare during pregnancy. systemic lupus erythematosus flare was defined as a change in disease activity as measured by SLEDAI score that required alteration in therapy. Each pregnancy was treated as an individual observation for analysis {14,15}.

Results

Table 1: Demographic Data of systemic lupus erythematosus patients-

Parameters		
Comorbidities	n	Percentage
Hypertension	2	15.38%
Diabetes	1	7.69%
Cardiovascular Disease	3	23.07%
Asthma	1	7.69%

Mean age of the 13 subjects was 27.2 and comorbidities for the same include Hypertension in 2, Diabetes in 1, cardiovascular disease in 3 and Asthma in 1 subject.

Table 2: Disease characteristics as per pregnancy –

Parameters	n	Percentage
Active disease at conception	2	15.38%
Antiphospholipid syndrome	4	30.7%
Systemic involvement		
Renal system- lupus nephritis	9	69.23%
Haematological	1	7.69%
Musculoskeletal	1	7.69%
CNS	1	7.69%

Table 2: Shows, 2 subjects with active disease at conception, 4 subjects with APLA syndrome and systemic involvement includes 9 subjects with lupus nephritis, 1 with haematological, 1 with musculoskeletal and 1 with CNS involvement.

Table 3: Maternal and pregnancy outcome

Parameters	n	Percentage
Live birth	8	61.53%
Still birth	4	30.76%
Miscarriage	1	7.69%
Fetal loss	5	38.46%
Pre-eclampsia	7	53.84%
Eclampsia	3	23.07%
Gestational diabetes	4	30.76%
Flare in pregnancy	3	23.07%
Preterm delivery	8	61.53%
Method of delivery		
LSCS	8	61.53%
Vaginal delivery	4	30.76%
Induced abortion	1	7.69%

Table 3 shows, 8 had live birth and 4 had still birth with 1 induced abortion, with 8 preterm deliveries. Fetal loss was seen in 5, Pre-eclampsia and Eclampsia in 7 and 3 subjects respectively, gestational diabetes in 4 and 3 subjects had Flare in pregnancy. LSCS was done in 8 and vaginal delivery in 4 subjects.

Table 4: Positive antibodies and treatment received in pregnancy

Parameters	n	Percentage
ANA	11	84.61%
Anti-ds DNA	7	53.84%
C3 complement	5	38.46%
C4 complement	3	23.07%
Lupus anticoagulant	1	7.69%
Anti-cardiolipin	3	23.07%
Anti – La	2	15.38%
Anti – Ro	1	7.69%
Treatment		
Prednisolone	11	84.61%
Azathioprine	5	38.46%
HCQ	8	61.53%
Cyclosporine	3	23.07%

Aspirin	11	84.61%
LMWH	5	38.46%

Table 4 shows 11 subject with ANA positive, 7 with Anti-ds DNA, C3 complement in 5, C4 compliment in 3, 1 with Lupus anticoagulant, 3 with Anticardiolipin antibody, 2 with Anti-La and 1 with Anti-Ro. 11 patients received treatment with tablet prednisolone and aspirin, 5 with azathioprine and LMWH, while 8 were put on HCQ and 3 received cyclosporin.

Table 5: Relationship between systemic lupus erythematosus characteristics and foetal outcome-

Systemic Lupus Erythematosus	Foetal Loss			Preterm delivery			Term delivery			
Parameter	N	Percentage	P-Value	n	Percentage	P-Value	n	Percentage	P-Value	N
Active disease at conception										
Yes	2	100%	0.019	1	50%	0.40	0	0%	0.029	2
No	3	27.3%		7	63.6%		4	36.4%		11
Lupus nephritis										
Yes	3	33.3%	0.063	5	55.6%	0.081	3	33.3%	0.09	9
No	2	50%		3	75%		1	25%		4
Flare in pregnancy										
Yes	2	66.7%	0.010	1	33.3%	0.175	1	33.3%	0.161	3
No	3	30%		7	70%		3	30%		10
APLS										
Yes	2	50%	0.31	3	75%	0.07	1	25%	0.246	4
No	3	33.33%		5	54.6%		3	33.4%		9

Table 6 – Relationship between systemic lupus erythematosus characteristics and maternal outcome-

Systemic lupus erythematosus	Systemic lupus erythematosus flare			Pre-eclampsia			Eclampsia			LSCS			
Active Disease at conception	N	%	p-value		%	p-value		%	p-value		%	p-Value	N
Yes	2	100%	0.029	0	0%	0.11	1	50%	0.012	0	0%	0.095	2
No	1	9.1%		7	63.6%		2	18.2%		8	72.7%		11
Lupus nephritis													
Yes	3	33.3%	0.056	4	44.4%	0.057	3	33.3%	0.32	5	54.6%	0.081	9
No	0	0%		3	75%		0	0%		3	75%		4
Flare up													
Yes	--	--		0	0%	0.088	2	66.7%	0.036	1	33.3%	0.133	3
No				7	70%		1	10%		7	70%		10
APLA													
Yes	0	0%	0.63	2	50%	0.091	1	25%	0.076	3	75%	0.552	4
No	3	33.3%		5	54.6%		5	54.6%		5	54.6%		9

Discussion

13 Pregnancies were analysed having systemic lupus erythematosus. Demographic data and disease characteristics have been charted in Table 1 and 2. Mean age of the study group was 27.2 ± 3.2. 15.38% of subjects were having Active disease at conception. More than half of the subjects had Lupus nephritis with a total of 69.23%. Table 3 illustrates maternal and foetal outcome. Live birth rate for our study was 61.53% while Foetal loss rate- 38.46%. Still birth loss was 30.76% and induced abortion at 19 weeks with a 7.69% and a total of Preterm deliveries were 61.53%.

The Gestational diabetes rate amongst our study group was 30.76%. Pre-eclampsia was observed in 53.84% and eclampsia in 23.07 % among which 61.53% underwent LSCS and 30.76 had a normal vaginal delivery.

Table 4. demonstrates presence of autoantibodies in our systemic lupus erythematosus patients and the treatment they received. Anti-Ro was detected in 7.69% and Anti la was detected in 15.38%. The mean C3 and C4 was - 38.46% and - 23.07% respectively. Majority of our patients were treated with Aspirin and prednisolone at about 84.61 % each and HCQ been given to 61.53%.

Table 5 and table 6 shows a relationship between fetal and maternal outcomes with systemic lupus erythematosus characteristics respectively. Women with active disease at the time of conception was evaluated to have a 3-fold rise in the incidence of fetal loss with a p value - 0.019 and a 10-fold rise in having a flare with a p-value of 0.029, with 2.5 times increase in the event of landing up into eclampsia having a p-value of 0.012 which are less than 0.5 and hence, statistically significant. Subjects who experienced a flare up during pregnancy had a 6-fold chances of eclampsia with a p value of 0.036- and 2-fold rise in incidence of fetal loss with a p value of 0.01, which are statistically significant.

Systemic lupus erythematosus is an autoimmune disease more commonly affecting females of younger reproductive age group in keeping with our study. Lupus nephritis was found in significant number of our subjects 69.23%, still the outcome of successful pregnancies was favourable as the patients had a regular follow up and treatment. We found Women with active disease at the time of conception was evaluated to have an increased risk of fetal loss of 100% which was higher than the studies of Malaysian cohort study of east Malaysia 92.35% {8}. We also found that the rate of systemic lupus erythematosus flare amongst our subjects were almost similar to the rate reported by Teh et Al (23.07 % vs 26.10 %) with a live birth rate of 61.53 % which was almost equal compared to the live birth rate 63 % and 61 % of China and Thailand studies respectively {6,9,16}.

One subject among the study group had a termination of pregnancy at the 19th week of gestation which was conducted due to a flare up of the disease with an underlying lupus nephritis and haematological system having a significant anaemia with poor cardiovascular function as she had a large pericardial effusion with a mild mitral regurgitation. She was treated with immunosuppressants and supportive management.

We had gestational diabetes which was 30.76% among our subjects out of which 84.61% patients were put on prednisolone during the gestational period, which was similar 33.87% to studies conducted by faculty of OBGY, kuala lumpur, Malaysia {16}.

Our LSCS rate of systemic lupus erythematosus patients were 61.53% which was most likely due to increased rate of complications such as pre-eclampsia and eclampsia which was 53.84% and 23.07%, which was second highest among the studies from south east Asia, highest being 64.2% {8,9}.

Women with active disease at the time of conception was evaluated to experience a 10-fold rise in rate of having a flare, which was 100 %, higher than the study of phansenee et al which noted 87.33% {9}. So, we can conclude that active disease at conception can be associated with adverse pregnancy outcomes like flare ups and eclampsia and fetal loss. 61.53% of our subject had a preterm delivery.

Hormonal and immunological changes in pregnancy are believed to affect systemic lupus erythematosus disease activity and animal model suggested that a rise in estrogen is linked to increased lupus activity. We found that on multivariable analysis, active disease at conception was a positive predictor of systemic lupus erythematosus flare in pregnancy amongst our study group. Several studies found that active systemic lupus erythematosus at conception and lupus nephritis were positive risk factors for flare in pregnancy. Flare in pregnancy specially lupus nephritis in the third trimester can be difficult to diagnose as it may be diagnosed as a flare when it actually could be pre-eclampsia as both can have proteinuria, reduction in serum albumin and mimic each other. Furthermore, C level used to determine disease activity can be difficult to interpret in pregnancy {4,7,8}.

Out of the lupus nephritis 69.23% subject, 44.4% experienced having preeclampsia in our study group, similar to the PROMISSE study of 45.77 % {17}. Clowse et al, found that the presence of Anti ds-DNA and low C levels in second trimester associated with increased rate of pregnancy loss and preterm birth which was equal to our study 53.85% {18}. lupus anticoagulant and Acl have been part of laboratory criteria for Sapporo classification of APLS and recent revision of international classification included antiphospholipid antibody. Our study showed that APLS was an independent risk factor for preeclampsia and carried a higher risk.

Low dose aspirin, heparin and prednisolone (84.61%) have been advocated in women with APLS with systemic lupus erythematosus to improve pregnancy outcome and had higher birth rates. So, in our study we practised to prescribe aspirin and heparin to all APLS patient who were pregnant 30.7 %. We found that in our study group that aspirin was associated with significant reduction in foetal loss but not in the rate of preeclampsia. An Italian study on pregnancy outcome in woman with pre-existing lupus nephritis found that aspirin had a protective effect against pregnancy loss. We prescribed HCQ to 61.53% subjects, which was associated with 20% reduced risk of pre-eclampsia {19}.

A Korean study on 179 pregnancies in 128 systemic lupus erythematosus patients discovered that discontinuation of HCQ predicted lupus flare which in turn associated with increased pre-eclampsia {20}. Earlier studies had shown a beneficial effect on HCQ on lupus activity during pregnancy and its thrombo-protective property is beneficial in reducing placental thrombosis and hence placental mediated complications. Based on our analysis, aspirin and HCQ should be routinely used in all pregnant systemic lupus erythematosus patients especially those with APLS. HCQ in particular should be the treatment of choice

especially in achieving remission in group of systemic lupus erythematosus woman considering pregnancy. Our study was limited by its retrospective nature and small sample size. Nevertheless, we had managed to successfully evaluate the relationship between systemic lupus erythematosus characteristics, presence of antibodies and treatment with pregnancy outcomes in systemic lupus erythematosus patients.

Inconclusion, our study demonstrated that active disease at pregnancy, flare in pregnancy, APLS is associated with adverse fetal and maternal outcomes. Pregnancy in systemic lupus erythematosus should be planned to reduce these adverse outcomes. Aspirin should be used in all systemic lupus erythematosus patients to reduce risk of foetal loss. HCQ and prednisolone seem to have a protective effect against pre-eclampsia and should be considered in all the women planning pregnancy.

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