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ORIGINAL ARTICLE

A Prospective Study to evaluate Pregnancy Outcomes in Patients with Systemic Lupus Erythematosus

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ABSTRACT

Aim: Study of systemic lupus erythematosus (SLE) with pregnancy to manage them in a multidisciplinary approach for better pregnancy outcomes.

Materials and methods: This study was a prospective cohort study. A total of 100 pregnant women with diagnosed SLE were included in the study and another 100 age-matched normal pregnant women without any obvious complications were recruited as controls.

Results: Maternal organ involvement—five patients of renal involvement and seven patients of cardiac and pulmonary involvement in SLE group—was found. Antinuclear antibody (ANA) was positive in all cases and 87 were positive for anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibody. The disease flare was found only in a single case of planned pregnancy and total nine cases of unplanned pregnancy. Most of the women, 41 (53.25%), in the SLE group were delivered by cesarean section, but only 24 (25%) in the control group underwent cesarean section.

Conclusion: The SLE with pregnancy is a high-risk condition where prepregnancy disease-free interval is the most important criteria to minimize complications. Hydroxychloroquine can be used safely throughout the pregnancy. Multidisciplinary approach plays a crucial part in management.

Clinical significance: Management of lupus flares and preeclampsia during SLE pregnancy is being treated with difficulties with overlapping clinical features. Presence of antiphospholipid antibodies (APLA) is a major unresolved issue. Adverse events to maternal and fetal well-being with use of appropriate medications are required for optimum outcomes.

Keywords: Adverse outcomes, Pregnancy, Systemic lupus erythematosus.

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INTRODUCTION

Systemic lupus erythematosus often affects women of reproductive age group with different complications starting from the various medical and obstetric complications. It has an overall incidence of (~1%) and higher in women with previous history of subfertility.[1] Lack of disease control and care prior to pregnancy may result in maternal death up to 20% cases mainly due to pulmonary embolism, cardiomyopathy, and failure of adrenal associated with abrupt cessation of steroids.[2] Often, complicated SLE like lupus nephritis may exaggerate in the course of pregnancy in the absence of prepregnancy 6 months disease-free interval and thereby pregnancy management may become difficult.[3] Presently, the live birth rate in pregnancy associated with lupus is approximately 70%.[4] Obstetric complications, such as spontaneous miscarriage, preterm labor, chorioamnionitis, preeclampsia, intrauterine growth restriction, and even maternal morbidity and mortality are major concerns of focus.[5] Neonatal complications like low birth weight, congenital heart block, neonatal lupus syndromes are also contributing to increased perinatal morbidity.[6] Being an autoimmune disease, some classical signs and symptoms like fatigue, fever, arthritis, photosensitive rash, serositis, vasculitis, Raynaud's phenomenon, glomerulonephritis, and hematological abnormalities are often encountered in the course of the disease.[7] Sometimes, normal pregnancy symptoms like chloasma, physiological proteinuria, gestational thrombocytopenia, pedal edema may be confused with the SLE exacerbations as malar rash, secondary proteinuria of preeclampsia, or intrinsic renal disease, thrombocytopenia of lupus exacerbation (thrombotic thrombocytopenic purpura), and lupus arthritis respectively.[8] In our study, we had studied 100 pregnant women with SLE who attended the institute which is a tertiary

Table 1: Comparison of baseline values

Parameters	*SLE with pregnancy (mean ± SD)*	*Healthy pregnancy (mean ± SD)*	*p-values*
Age (years)	25.4 ± 3.495	24.92 ± 3.440	>0.05
Duration of marriage (years)	4.6 ± 2.933	4.1 ± 3.816	>0.05
Duration of disease (years)	3.8 ± 2.112	–	–
Gestational age (weeks)	28.30 ± 9.080	36.18 ± 3.088	<0.001
Birth weight (gm)	2,186.3 ± 315.05	2,751.7 ± 430.34	<0.001
Hemoglobin (gm/dL)	9.6 ± 0.806	11.1 ± 0.639	>0.05
TLC (per cu mm)	8,465.3 ± 2,862.7	6,670.6 ± 1,454.7	<0.001
Thrombocyte count (per cu mm)	124,476 ± 11,453.5	367,548 ± 10,751.7	<0.001
ESR (mm/hr)	94.70 ± 15.23	36.86 ± 10.98	<0.001
Serum urea (mg/dL)	34.8 ± 3.854	29.46 ± 4.067	>0.05
Serum creatinine (mg/dL)	1.2 ± 0.267	0.88 ± 0.312	>0.05

care center with the aim to manage them in a multidisciplinary approach for better pregnancy outcomes.

MATERIALS AND METHODS

It was a prospective cohort study. A total of 100 pregnant women with diagnosed SLE were included as case. Case was defined by criteria laid down by the American College of Rheumatology.[9] The cases were selected from the Rheumatology and Obstetrics clinic from 2006 to 2016. We had randomly selected another 100 age-matched normal pregnant women without any obvious complications as controls from the obstetrics clinic. The medical management of all these patients were done by rheumatologists and pregnancy-related care was provided by the obstetrician. The pregnancy outcomes were noted. Relapse or flare-up was defined as acute serositis, synovitis, pruritus, dermatitis, new onset of psychological or neurological symptoms, and deranged hematological parameter like leukopenia, thrombocytopenia, or active renal disease during pregnancy and requiring inpatient care. Renal involvement was defined as proteinuria ≥300 mg/day (in the absence of gestational hypertension), cell casts in urine and hematuria. All the patients were reviewed at the Lupus Clinic (jointly by Obstetrics and Rheumatology Department) for further 6 months after child birth in postnatal period.

RESULTS

Our study comprised of 100 pregnant women with SLE. As in Table 1, the mean age of the SLE women was 25.4 ± 3.495 *vs* 24.92 ± 3.440 years in the control group ($p > 0.05$). Duration of marriage was 4.6 ± 2.933 years in SLE patients *vs* 4.1 ± 3.816 years in the control group ($p > 0.05$). Duration of gestation was significantly lower in SLE women 28.30 ± 9.080 *vs* 36.18 ± 3.088 weeks in the control group ($p < 0.001$). There was significantly low fetal birth weight of 2,186.3 ± 315.05 gm in SLE mothers *vs* 2,751.7 ± 430.34 gm ($p < 0.001$) in healthy mothers. Blood pictures of SLE mothers as per Table 1 showed no difference in hemoglobin 9.6 ± 0.806 *vs* 11.1 ± 0.639 gm/dL in healthy pregnant women ($p > 0.05$), serum urea 34.8 ± 3.854 *vs* 29.46 ± 4.067 mg/dL in healthy pregnant women ($p > 0.05$), and serum creatinine 1.2 ± 0.267 *vs* 0.88 ± 0.312 mg/dL in healthy pregnant women ($p > 0.05$). In SLE women, significantly higher total leukocyte count (TLC) 8,465.3 ± 2,862.7 *vs* 6,670.6 ± 1,454.7 per cu mm in the control group ($p < 0.001$), lower platelet count 124,476 ± 11,453.5 *vs* 367,548 ± 10,751.7 per cu mm in the control group ($p < 0.001$), and erythrocyte sedimentation rate (ESR) 94.70 ± 15.23 *vs* 36.86 ± 10.98 mm/hour in the control group ($p < 0.001$) were observed. Maternal organ involvement as depicted in Table 2 shows 5 patients of renal involvement in the SLE group and only single in the control group, 7 patients of cardiac and pulmonary involvement in the SLE group and only 2 in the control group who suffered from rheumatic heart disease, 21 patients of arthritis, 20 patients of cytopenia (hemolytic anemia, leukopenia, and thrombocytopenia) were found in the SLE group. Antinuclear antibody was positive in all cases and 87 were positive

Table 2: Organ involvement and immunological status in SLE patients (n = 100)

Parameters		*SLE pregnancy*	*Healthy pregnancy*
Renal disease		5	1
Cardiac and pulmonary involvement		7	2
Arthritis		21	Nil
Cytopenia (hemolytic anemia, leukopenia, thrombocytopenia)		20	Nil
Positive anti-dsDNA antibody		87	Nil
Positive ANA		100	Nil
Flaring of disease during pregnancy	Planned pregnancy	1	Nil
	Unplanned pregnancy	9	Nil
Association with APLA		20	2
Preeclampsia		26	5

Table 3: Fetal outcome in SLE pregnancies compared with healthy pregnancies (n = 100)

Parameters		*SLE pregnancy*	*Healthy pregnancy*
Spontaneous miscarriage		23	4
Intrauterine fetal death		8	2
Preterm birth		37	8
Term live birth		32	86
Mode of delivery (excluding miscarriage)	Vaginal	36 (46.75%)	72 (75%)
	LSCS	41 (53.25%)	24 (25%)

LSCS: Lower segment cesarean section

for anti-dsDNA antibody. There were 20 SLE women who also suffered from APLA, whereas only two in the control group suffered from APLA. Preeclampsia was found among 26 SLE women, whereas it was found only in 5 women in the control group. The disease flare was found only in a single case of planned pregnancy and total nine cases of unplanned pregnancy. Table 3 shows increased adverse fetal outcomes in SLE patients compared with the control group. Spontaneous miscarriage was in 23 cases *vs* 4 cases in the control group. Preterm birth was among 37 SLE women *vs* 8 healthy women, and term birth was in 32 SLE women *vs* 86 healthy women. Totally eight cases of intrauterine fetal death in SLE women were noted, but only two cases of intrauterine fetal death were noted in the control group. Vaginal delivery occurred only in 36 (46.75%) women in the SLE group *vs* 72 (75%) women in the healthy group. Most of the women (41, 53.25%) in the SLE group were delivered by cesarean section, but only 24 (25%) in the control group underwent cesarean section.

DISCUSSION

Systemic lupus erythematosus with pregnancy is a condition with increased maternal and fetal morbidity and mortality. Preconceptional care is the most important aspect in this regard. It starts from the counseling up to medical management and advanced care. Commonly, the risk of fetal loss, preterm birth, intrauterine growth restriction, and neonatal lupus syndromes may not be easy to overcome. Lupus flares, pregnancy-induced hypertension (PIH), and other complications, such as preterm labor, thrombophlebitis, and sepsis often hassle the course of pregnancy.[10] The risk of preterm birth and low birth weight baby is more in lupus patients than in normal pregnant women.[11] Our study also showed that the mean gestational age of the study group is less than term and the mean birth weight of the babies was less than 2500 gm. Increased TLC, thrombocytopenia, and increased ESR are usually seen in SLE patients as in our study. Rise in apoptotic polymorphonuclear cell, macrophage, and altered immune tolerance by the macrophage are contributory to raise the TLC and ESR in the absence of tissue transglutaminase receptor, which acts as a pivot in apoptosis of phagocytic cells.[12] Thrombocytopenia is immune-mediated destruction and sometimes associated with microangiopathic hemolytic uremic syndrome.[13] Lupus flare which is exacerbation of disease activity is more in unplanned pregnancies. Active disease activity at the time of conception in unplanned pregnancies is responsible for exaggerated adverse pregnancy outcomes.[13] Multiple organ systems are involved in SLE like cardiac, renal, musculoskeletal, and pulmonary, and also have variable responses, but renal involvement is more common than the other systems.[14]

Several autoantibodies are found in lupus patients like APLA, anticardiolipin, and anti-b2 glycoprotein antibodies, which are responsible as autoantibodies against their tissue-binding proteins. Intercross activities of many autoantibodies and overlapping of clinical conditions, such as anemia, low platelet count, and proteinuria can contribute to the diagnostic dilemma.[15] The use of hydroxychloroquine during pregnancy in women with lupus is beneficial. Though it is a category C drug in pregnancy (US Food and Drug Administration), it reduces disease activity and flare in pregnancy without any obvious major adverse effects on the fetus.[16] Congenital heart block and neonatal lupus syndromes are also significantly reduced with the use of hydroxychloroquine in lupus pregnancy. But we did not find any case of neonatal lupus in our study.

We found in our study association with APLA in 20% cases. Lupus is a risk factor of developing PIH. Diagnosis of PIH remains difficult because of similar scenarios like nephritis presenting with proteinuria, deranged renal function, preexisting hypertension, and low platelet count. Preeclampsia was documented in 26% cases in lupus pregnancy. Low sensitivity and specificity biomarkers like placental growth factor, soluble fms-like tyrosine kinase-1, and soluble endoglin as screening markers of preeclampsia restrict their use as clinically effective predictor tools.[17]

Antinuclear antibodies are most commonly used as a screening tool in lupus. It binds with the elements in the nucleus of cells and which is known as nuclear antigen. The sensitivity of ANAs is very high as a screening tool which is about up to more than 95%.[18] But we had found in our study that all SLE patients were positive for ANAs. Anti-double-stranded DNA antibodies are more specific than ANAs, but are carrying lower sensitivity (60%). We have found anti-dsDNA in 87% cases in our study. Both ANA and anti-dsDNA are sensitive and specific for diagnosing lupus, particularly for those patients who are asymptomatic or having other connective tissue diseases.[18]

Adverse perinatal outcomes like spontaneous abortion, stillbirth, preterm birth, low birth weight, neonatal lupus, and maternal complications are major concern in lupus pregnancy. Although lupus patients are comparable from fertility point of view as women in the general population, the pregnancies are associated with complications.[19] Prior 6 months of disease-free interval before conception is essential for improving pregnancy outcomes. Contraception and family planning are both important for women with lupus. Maternal health and fetal development should be monitored during pregnancy. If possible, delivery should occur in a multidisciplinary facility.[20]

CONCLUSION

Pregnancy in women with SLE is a high-risk condition. In spite of considerable improvement in success rates, high maternal and fetal morbidity and mortality remain a major concern. Disease activity may increase during the pregnancy.

CLINICAL SIGNIFICANCE

Recognition and treatment of disease flares and preeclampsia during SLE pregnancy are being handled with difficulties including overlapping clinical features, lack of diagnostic markers, and drug toxicities. Increased fetal loss, especially in the presence of APLA, is a major unresolved issue. The key to success lies in the multidisciplinary care with close monitoring. Early detection of adverse events to maternal and fetal well-being with use of appropriate medications is required for optimal pregnancy outcomes.

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