

Original Article

# Systemic Lupus Erythematosus and Pregnancy Outcome in Tertiary Level Hospital of Nepal

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## ABSTRACT

**Introduction:** Systemic Lupus Erythematosus is an autoimmune disease frequently prevalent in women starting from early childhood and towards the reproductive age. Pregnancy with SLE has always imposed great risk both to the mother and the fetus. A multidisciplinary approach with nephrologist, neonatologist and senior obstetrician during remission leads to a favorable response, through limitation and complications with the use of drugs impose difficulties in their management.

**Materials and Methods:** A prospective, descriptive study was conducted in the Department of Obstetrics and Gynecology and Nephrology at Tribhuvan University Teaching Hospital, for 2 years, from June 2015 to 2017. The study included obstetrical and related complications with outcome in pregnant patients with Systemic Lupus Erythematosus.

**Results:** A total of 19 cases were analyzed of which 15 (79%) had a viable pregnancy and 4 (21%) abortions. Of thirteen cases, 4 (21%) had antiphospholipid antibody syndrome, 8 (42.1%) lupus, and membranous glomerulonephritis and 1 (5.2%) lupus optic neuropathy with loss of vision. All the patients were under drug therapy, like prednisolone, azathioprine, hydroxychloroquine, aspirin, low molecular weight heparin, tacrolimus, and cyclophosphamide. Only 2 (10.5%) of 19 developed severe pre-eclampsia. There were 12(80%) term and 3(20%) each of preterm and intrauterine growth retardation pregnancies with 1(6.6%) neonatal death (NND) and 1(5.2%) maternal mortality.

**Conclusions:** Multidisciplinary approach and planned pregnancy reduces the risk of probable complications in the patient resulting to a decreased morbidity and mortality.

**Keywords:** Abortion; Anti-phospholipid antibody; Glomerulonephritis; Pre-eclampsia; Pregnancy; Systemic Lupus Erythematosus

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## INTRODUCTION

Systemic Lupus Erythematosus (SLE), a chronic inflammatory autoimmune disease affecting any organ of the body and follows a course of relapse and remission. It is frequently prevalent in women starting from early childhood and towards the reproductive age.<sup>1</sup> The triad of fever, joint pain and rashes in a woman of childbearing age should prompt for investigation into SLE diagnosis. Pregnancy with SLE has always imposed

greater risk to the mother and the fetus. Although live births are achieved in majority of pregnancies, active disease and major organ involvement requires more vigilant monitoring. Pregnancy in active state has usually led to unfavorable outcome, thus preconceptional counseling and advocacy of pregnancy post 6 months of quiescent phase is advised.<sup>2,3</sup>

Maternal complications like flare up of disease, preeclampsia (PE) is common during pregnancy. Complications like pre-term birth, intra-uterine growth restriction (IUGR), neonatal lupus syndromes, and congenital heart blocks are major fetal issues. Fetal loss following anti-phospholipid antibody syndrome (APLA) and other early pregnancy complications are quite common concern.<sup>1</sup>

Limitation and complications in the use of drugs furthermore imposes restrictions in their management. Multidisciplinary approach with Nephrologist, Neonatologist and Obstetrician with favorable medication, close monitoring and vigilant watch for complications can lead to lesser maternal and fetal morbidities and mortalities.<sup>4</sup> Hence, with this study we aimed to study the obstetrical outcome of pregnancy and related complications among SLE patients.

## MATERIALS AND METHODS

A prospective, descriptive study was conducted in the Department of Obstetrics and Gynecology and Nephrology at Tribhuvan University Teaching Hospital, (TUTH) for 2 years, from June 2015 to 2017. Diagnosis of SLE was established by the Nephrology department based on the criteria by American College of Rheumatology. The established SLE cases at any period of gestation were included. Permission from the department and ethical clearance from Institutional Review Board was obtained. Adherence with the tenets of Declaration of Helsinki maintained.

Regular blood and urine examinations like CBC, Hb%, platelet, ESR, Prothrombin time, RFT (Urea, Creatinine, Na, K), LFT (Bilirubin, total protein, AST, ALT, Alkaline phosphatase, LDH), Urine RE/ME were done in all cases. Anti cardiolipin antibody (APLA) and Lupus anticoagulant were done in selected cases. Anomaly and sequential abdominal ultrasonography scans were done in all cases as required. USG Doppler study was done to rule out IUGR. Fetal echocardiography was done as per need.

Data were entered and analysed in Microsoft Excel.

## RESULTS

A total of 19 cases were studied in a span of 2 years. Duration of SLE varied from 6 months to 10 years.

### Antenatal Checkup, investigations and follow ups

Though fifteen (79%) of the 19 patients had uneventful pregnancy, viable outcome was seen only in 14 (74%) despite of many hardships. Nine of 19(47.3%) cases had one or multiple antenatal checkups and 4(21%) cases were referred, with antenatal checkup visit ranging from 4+ to 26+ weeks. A total of 15 (79%) patients had regular blood and urine examinations but 4(21%) cases who needed manual vacuum aspiration (MVA) for abortions or blighted ovum had more frequent and additional investigations. Anti cardiolipin antibody (APLA) was positive in 4 (21%). USG Doppler study was done to rule out IUGR. Fetal echocardiography done in 9 of 15 (60%) cases was normal.

### Drug Therapy

Among 19 patients, 17 (89.47%) patients were treated with Prednisolone (2.5 - 40 mg) throughout pregnancy with average of maintenance dose of 5 mg. Azathioprine 50 mg was prescribed to 11 (57.8%) patients, prior to conception and continued throughout. Hydroxychloroquine 200 mg was given to 16 (84.2%) patients. Aspirin (13, 68%) in low dose of 75 mg was given as prophylaxis against PE/eclampsia, was continued till 34 weeks. Of the 4 APLA positive cases, 2 patients were started on aspirin and low molecular heparin, rest 2 cases received aspirin only. Injection tacrolimus was given to the patient with membranous glomerular nephritis with 24 hour urinary protein of 3907mg. Tacrolimus was added to her existing drug and the blood level of tacrolimus was done regularly that led to a favorable outcome. One patient received Inj. Cyclophosphamide and Enalapril prior to conception and preterm delivery of 29-30 weeks, however both mother and baby deceased. Both these drugs were stopped once pregnancy was diagnosed. Other than these, antihypertensive drugs like Amlodipin, methyldopa, glyceryl trinitrate were given as required in patients who developed PE.

### Presence of Antiphospholipid antibody syndrome, lupus nephritis and membranous glomerulonephritis, Lupus optic neuropathy

Four (21%) of 19 patients were diagnosed to have APLA positive. Of these 4 patients, 2 had favourable outcome. Lupus nephritis was diagnosed in 8 of 19 (42.1%) patients prior to conception. One of 8 had a history of pancytopenia, lupus nephritis that needed ICU admission for 21 days with transfusion of 5 pints of whole blood and 21 pints of fresh frozen plasma. Two of 8(25%) had membranous glomerular nephritis as well.

A case of APLA positive SLE lupus nephritis (class III) with active proliferating chronic sclerosing lesion with hypertension came at 26+ week pregnancy. She complained of loss of vision for 2 days and was diagnosed as Lupus optic neuropathy. She was on prednisolone, aspirin, Inj heparin, ACE inhibitor, hydroxychloroquin and calcium. She had received 6 cycles of Inj Cyclophosphamide 3 years back. MRI was done, which showed post reversible encephalopathy syndrome. She regained her vision in a week time from 2/60 to 6/12. She was anaemic with 8.3 gm% hemoglobin, thrombocytopenia (platelet-60,000/cumm), deranged renal functions and blood sugar. She was advised for blood transfusion along with Inj Cyclophosphamide but the patient party opted to take her home against medical advice. The next day she had fatal outcome. Rests of the patients were in the remission phase during their pregnancies, thus leading to a good outcome.

### Obstetric outcome

Due to early booking and regular follow up, most of the patients did well throughout their pregnancy. A watchful eye was kept on the blood pressure monitoring, along with regular blood and urine tests in every antenatal visit. The follow up was scheduled 2-4 weekly and as per the urgency.

### Previous obstetric history

Nine of 19 patients (47.3%) had history of previous abortions. Two of 9 (22.2%) had recurrent blighted ovum and 1(11.1%)

was with history of incomplete, 2 recurrent abortions and 1 still birth of 7 months. Another 4 of 9 (44.4%) had history of 1-2 spontaneous losses in early gestations of 6-8 weeks. Rest 2 of 9 (22.2%) were induced abortions done for severe proteinuria and for reasons unknown.

### Severe Preeclampsia

Two of 19 (10.5%) developed severe pre-eclampsia. One with severe PE taking methyldopa and nifedipine developed IUGR, required early termination at 29 weeks, with favorable outcome. Another was young primigravida at 17+ weeks with severe PE, acute kidney injury and severe anaemia requiring blood transfusion. She was on methyl dopa, amlodipine, glyceryl trinitrate. USG diagnosed missed abortion that was managed with medical termination with misoprostol.

### Present Obstetric History

#### Abortions

In index pregnancy, 4 of 19 (21%) patients had abortions. One of them had recurrent blighted ovum in a 2nd gravida and was APLA positive. She underwent MVA at 8+ weeks due to abortion. Of the other 3, 2 had missed abortions at 11+ weeks requiring MVA and at 17+ weeks with severe PE, AKI and anaemia requiring medical termination with misoprostol. The last case was a G5 P2+2 L1 at 22+ weeks with CKD with Lupus Nephritis with anaemia. She hadn't had any antenatal checkup with only 1 living issue, a male of 3 years, following death of a female child due to probable cerebral palsy and other 2 previous induced abortions. On admission her Hb was 7.6gm%, urea 19.3 mmol/l and creatinine was 467 mg/dl. She was taking tab corticosteroid, inj. Lasix and had undergone 6 cycles of haemodialysis on biweekly basis. USG showed live pregnancy of 22-23 weeks. After receiving 3 pints of packed cell, termination with misoprostol was done. She expelled a single dead female of 475 gm and later was discharged in good health.

#### Preterm, IUGR and Perinatal Mortality

Of 19 cases, 3 (15.7%) had preterm vaginal deliveries. The first was a referred case at 26+ weeks. She was diagnosed as SLE with mixed connective tissue disorder, severe PE, with idiopathic thrombocytopenic purpura (ITP) and with hypothyroidism for the likelihood of early termination and the possibility of neonatal care. She was on Tab. nifedipine 20 mg TDS and Tab. methyldopa 500 mg QID. Inj. dexamethasone was given for fetal lung maturity. Ultrasonography with the Doppler study showed abnormal study needing premature termination with tab misoprostol. She had a preterm vaginal delivery with an outcome of a female of 1.1 Kg and was discharged later in good health. Other patient was Primigravida at 34+4 weeks with premature rupture of membrane for 24 hrs. She received Inj dexamethasone and had a preterm vaginal delivery with of a female child of 1.9 kg with good APGAR score.

A known case of SLE nephritis (class III) with APLA with lupus optic neuropathy with chronic HTN at 26-27 weeks pregnancy went into labour at 30 weeks with PV leaking and delivered a female weighing 750 gms with 6/10 7/10 APGAR score. Patient and her relatives refused to resuscitate the baby following which the baby died on the 3<sup>rd</sup> day of life.

Other 3 patients had term deliveries, at 40+1, 37+2 and 37+1 weeks respectively, but they were IUGR babies with the birth weight of 2.3Kg, 2.4 kg and 1.8 Kg respectively and with good APGAR score.

### Mode of delivery

Fifteen of 19 (79%) had delivered either vaginally (n=7; 46.6%) or through lower segment Caesarean section (LSCS) (n=8; 53.3%). Fourteen of 15 patients had favorable outcome. Of the 15 patients, 8 (53.3%) had LSCS and 7 (46.6%) had vaginal delivery. The indications of LSCS were thick meconium stained liquor (n=2), persistent fetal tachycardia (n=1), and fetal bradycardia (n=1), and 1 each for previous LSCS, oligohydramnios and 2 each elective LSCS for bad obstetric history.

Of the 7 patient with vaginal delivery, 3 were preterm deliveries (2 were induced) of which one was following premature rupture of membrane for 24 hours at 34+4 weeks and the other was at 26+ weeks delivered an extreme low birth weight baby and the last was a spontaneous preterm vaginal delivery at 30 weeks following per vaginal leaking leading to neonatal death on the 3<sup>rd</sup> day of life.

### Fetal outcome

There were 4 abortions and 15 viable pregnancies in a total of 19 cases studied, of which, favorable outcome was observed in 14 of 19 (73.68%) pregnancies. Twelve of 15 (80%) were term and 3(20%) were preterm pregnancies and all had good APGAR score. The maximum birth weight was 3 Kg and the least was 750gms. Two of the 15 babies (13%) required neonatal care. One baby was admitted for persistent vomiting but later recovered and was discharged on the 8<sup>th</sup> post partum day. Another was the preterm IUGR (1.1kg) who needed longer neonatal stay of 38 days for neonatal meningitis and Klebsiella sepsis. but later was discharged in good health. There were no intrauterine fetal deaths but an early neonatal death was observed in 1 case, though pregnancy loss was observed in 4 patients. Fetal ECHO was done in 9 of 15 (60%) cases were normal. There were no cases of congenital heart block or neonatal lupus seen.

### Disease Flare

Of the 19 reported cases there was only 1 maternal mortality which occurred on the 10<sup>th</sup> post-partum day following preterm vaginal delivery, that could be attributed to flare up of the disease condition

### Perinatal and maternal Mortality

There was one perinatal and one maternal death. A 27 year primigravida at 26-27 weeks, a known case of SLE nephritis (class III) with APLA for the past 8 years with lupus optic neuropathy with chronic HTN, presented to ER with pregnancy of 6 months, headache and facial puffiness for 1 week along with loss of vision for 2 days. She was on prednisolone, losartan, hydroxychloroquine, aspirin. She was diagnosed as Lupus nephritis with active proliferative and chronic sclerosing lesion class III in her renal biopsy for which she received 6 cycles of inj cyclophosphamide. This was a planned pregnancy, which she conceived after consultation with the physician. She was on tab emsolone, hydroxychloroquine, azathioprine, ACE inhibitor,

aspirin, calcium was only stopped prior to conception. She had 5 ANC in local hospital outside Kathmandu. She was also taking Iron and calcium and was immunized with Inj TT. Anomaly scan and fetal ECHO was not done.

On arrival to the hospital, she was irritated but her vitals were stable. Her fundal height was 24 weeks and fetal heart sound was heard with Doppler. Ophthalmological consultation was done that was suggestive of Lupus optic neuropathy and anaemic retinopathy. Investigation showed Hb 8.3gm%, platelets 60,000/cumm, RFT and blood sugar was deranged too. MRI showed features suggestive of post reversible encephalopathy syndrome. Inj Prednisolone, Hydroxychloroquine, Azathioprine, amlodipine were continued. She was under continuous monitoring and she regained her vision after about 1 week.

At 29-30 weeks (3 weeks later), she complained of PV leaking and was already in active stage of labour and could not be arrested. She delivered a female weighing 750 gms with 6/10 7/10 APGAR score. Patient and party refused for surfactant and to keep the baby in NICU, following which the baby died on the 3<sup>rd</sup> day of life.

Her haemoglobin level started to fall from 8.3 gm% to 7.1 gm%, following which she received 2 pint of blood transfusion. As her platelet was on the lower side, her antiplatelet drugs were on hold and again inj cyclophosphamide was started and her haemoglobin increased. Her condition deteriorated. On 10<sup>th</sup> postpartum day the patient left against medical advice.

## DISCUSSION

Pregnancy in patient with SLE always has had the fear of embarking on some sort of morbidities and not to forget the neonatal complications that can develop too. The time of conception after the diagnosis of the disease was from 6 months to 10 years with almost 100% of them being in remission phase in our study. Thus one of the main factors that had lead to favorable outcome in the study could be the state of remission. Studies also suggest that the outcomes of lupus pregnancies are better if pregnancy is delayed until the disease is in a quiescent state for at least 6 months.<sup>5</sup> Also the medication adjusted in advance has the advantage of enduring pregnancy till term with a positive outcome.<sup>3</sup>

Though preconceptional counseling has a vital role; none of the patients seek for it. Nine of 19(47.3%) cases were either booked or supervised and only 4(21%) cases were referred, thus contributing to a favorable outcome in 68% cases. Similarly improved pregnancy outcome was seen in a study conducted by Khamashta MA in a tertiary level hospital with multidisciplinary experienced team.<sup>4</sup> The crux is, improved pregnancy outcome could be anticipated with a multidisciplinary experienced team in a tertiary level hospital like TUTH.

As all of the 19 patients were diagnosed with SLE prior to pregnancy. Investigations in 15(79%) patients, including the 4(21%) who had abortion, were done as advised by nephrologist to assess the disease activity and damage as required and as advised by the nephrologist as in other studies.<sup>6</sup> Antiphospholipid antibody syndrome, lupus and membranous glomerular nephritis are few of the unwanted manifestations that can be seen in

patients with SLE. Fetal loss, chances of preterm labour, IUGR, were significantly higher in patients with APLA than without.<sup>1,7</sup> Of 19 patients, 4 (21%) were diagnosed with APLA and 8 (42.1%) had lupus nephritis of which 2 had glomerular nephritis. None of these patients had any complications. Of the 4 patients, 3 had favourable outcome and 1 needed MVA during her previous pregnancy for severe proteinuria of 5 gm. Similar findings were observed in other study done by Rehman et al.<sup>8</sup>

Prednisolone, in the dose ranging from 2.5-40 mg was given to almost all the patient (89% (17/19) that was started prior to conception and was continued throughout in a maintenance dose of 5mg. A study conducted by Wang YH et al concluded that the rates of PE and fetal losses were more in the patients taking prednisone more than 20 mg/day compared to patients taking less than 15 mg/day.<sup>9</sup> Contrary to this the favourable outcome in the present study could be attributed to the low maintenance dose of Prednisolone that the patients were on.

Hydroxychloroquine treatment was associated with a higher rate of live births with spontaneous vaginal delivery and lesser proportion of spontaneous abortions and placenta-mediated complications<sup>10</sup> and in our study, 84%of patients were under HCCs. Azathioprine (50 mg), is a safe and non teratogenic drug which was given to 11 of 19 (58%) patients prior to conception and continued throughout.<sup>11</sup> Azathioprine is one of the only few immunosuppressive agents that has documented safety during pregnancy. The dose should be limited to maximum of 2mg/kg/day, to avoid risk of fetal cytopenias.<sup>12</sup>

Only 1 patient received tacrolimus, who was previously diagnosed as membranous glomerular nephritis with severe proteinuria of 5 gm that persisted during the antenatal period too. Addition of tacrolimus around second trimester could be credited for her favourable outcome though no controlled trials looking at its use in pregnancy suggest potential efficacy and safety, but the long term outcomes are more supportive by its addition as it is very effective at reducing proteinuria and keeps the disease in a stable state, which was evident in this study too.<sup>13,14</sup> Though 1 patient was on cyclophosphamide, it was immediately stopped once her pregnancy was diagnosed, as it is thought to have an adverse effect as well as unfavourable outcome in these complicated pregnancies<sup>15</sup> Ocular involvement inform of lupus retinopathy and lupus optic neuropathy has been reported in earlier report from Nepal.<sup>16</sup>

Addition of aspirin 75 mg, which is thought to be an individual predictor of favourable outcome was given to 68% of the patients that probably prevented them (13/19) from developing PE<sup>17</sup> amlodipine, methyldopa, glyceryl trinitrate were the antihypertensive drugs that were used in patients who developed PE. Antihypertensive drugs need to be given with caution in patients with hypertension weighing the benefit and the risk of giving it.<sup>18</sup>

Fetal and neonatal complications are also quite high in these high risk pregnancies; especially neonatal SLE carries a significant morbidity and mortality when the fetal heart is the targeted organ.<sup>4</sup> Fetal ECHO was done in 6 of 12 (50%) viable pregnancies and none of the neonates were found to have any sort of heart lesions though the incidences of congenital heart blocks have been stated.<sup>19</sup>

Most of the patients had history of pregnancy loss either in the

form of abortions or blighted ovum. Nine (47%) of 19 patients had history of previous blighted ovum and missed, induced or spontaneous abortions; consistent to study by Park et al.<sup>20</sup> Even in index pregnancies 4 of 19 (21%) had blighted ovum, missed abortion and 1(25%) G5 P2+2 L1 at 22+ weeks with CKD with lupus nephritis with anemia needed termination as reported in other studies.<sup>21</sup>

Incidences leading to preterm delieveris, IUGR and intrauterine fetal demise have been acknowledged.<sup>22</sup> About 10-30% of SLE pregnancies are complicated with fetal growth restriction and small for gestational age babies.<sup>23</sup> Of 19 cases, 3 (15.7%) had preterm vaginal deliveries with IUGR and 3 (15.7%) were term deliveries but with IUGR babies with good APGAR score. Preterm vaginal delivery and IUGR were seen more in cases with severe PE and lupus nephritis.<sup>24</sup>

Of the 15 patients, 14(93.3%) had good outcome, of which, 8 (53.3%) had caesarean section and 7 (46.6%) vaginal delivery.

More caesarean sections were done for obstetric indication than for SLE related complications as evident by maximum number of emergency (6, 75%) than elective sections (2, 25%). There was only 1 maternal mortality compared to a National study done by Megan E. B. Clowse et al stating a 20 fold increase in mortality in women with SLE.<sup>25</sup>

## CONCLUSIONS

Systemic lupus Erythematosus manifestations are protean and can impact the pregnancy outcome. A coordinated multidisciplinary approach by the Rheumatologist, Nephrologist, Ophthalmologist, Obstetrician and Neonatologist can lead to favourable pregnancy outcome. Thus it is advisable to plan the pregnancy and discuss the management strategy and probable complications with the patient to increase the successful outcome.

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