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Effectiveness of pre-conceptional counselling in preventing adverse maternal and fetal outcomes among pregnant women with Systemic Lupus Erythematosus: A prospective observational study

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is an idiopathic, chronic autoimmune inflammatory disease with a high prevalence in females of reproductive age group. In the past, SLE patients were advised not to become pregnancy because of poor maternal and fetal outcomes. But nowadays the scenario has been changed because of pre-conceptional counselling and intense surveillance of disease during and after pregnancy. To study the effectiveness of pre-conceptional counselling in preventing adverse maternal and fetal outcomes among pregnant women with Systemic Lupus Erythematosus.

Materials and methods: It is a prospective observational study conducted among 32 women who were diagnosed with SLE and confirmed for pregnancy. Among these 32 women, 14 women have received pre-conceptional counselling and remaining 18 women did not receive pre-conceptional counselling prospectively. Maternal and fetal outcomes includes incidence of pre-eclampsia, lupus flare,f etal losses, fetal growth restrictions(FGR),preterm labor, neonatal lupus and oligohydramnios.

Results: Total of 32 SLE pregnancies were studied. The incidence of SLE in this hospital was 0.79 per 1000 pregnancies (32 out of 40032). 14 (43.7%) of women received pre-conceptional counselling,18 (56.2%) did not receive pre-conceptional counselling. Among women who received PCC 5(35.7%) cases developed late onset pre-eclampsia without severe features,3(21.4%)fetal wastage, 3 (21.4%) cases were pre term labour and 3 (21.4%) cases were diagnosed as FGR. Among women who did not receive PCC 9 (50%)cases developed pre-eclampsia, 9 (50%)fetal wastages 6 (33.3%) cases were pre term labour and 6 (33.3%) cases FGR were diagnosed.

Conclusions: Adverse maternal and fetal outcomes like preeclampsia, pre term labor, FGR, lupus flare and fetal wastage were high among women who did not receive pre-conceptional counselling compared to women received. Pre-conceptional counselling decreases the adverse outcome of the disease to large extent.

Keywords: Pregnant Women**,** Systemic lupus erythematosus (SLE), pre-conceptional counselling, Maternal and fetal outcomes

INTRODUCTION

SLE is an autoimmune mediated disease which affects the women of reproductive age group. SLE is variable in its presentation- can present as fatigue, malaise, arthralgias, skin rashes (discoid, malar), lymphadenopathy, nephropathy, effusions, seizures, haematological (anaemias, thrombocytopenia, leucopenia). SLE is diagnosed based on Revised American College of Rheumatology classification criteria. SLE in pregnancy can be considered as high risk because it affects both maternal and fetal mortality and morbidity. Mother with SLE can face increased incidence of preeclampsia, lupus flares, thrombotic episodes, fetal wastages. Fetal complications are increased incidence of fetal losses, preterm birth, IUGR, neonatal lupus syndrome.[1]

SLE needs a multidisciplinary approach by gynaecologist, rheumatologist, neonatologist. Pre-conceptional counselling is mandatory, during this the team should assess each organ function, pregnancy is not advised if there is any contraindication (advanced renal insufficiency, pulmonary hypertension, severe restrictive lung disease, heart failure), assess the disease status (high activity leads to poor pregnancy outcome), assess the autoantibodies especially APLA, anti-Ro, anti La, review the medications, adjust the dosage to get good disease control. Disease free interval of 6 months is needed to get better outcome. Azathioprine, hydroxychloroquine, prednisolone are commonly used drugs.[2]Cyclophosphamide, mycophenolate mofetil is used if disease is not controlled with above drugs. Lupus flare is treated with high dose glucocorticoids. Methyl prednisolone 1000 mg IV for 90 min for 3 days.[3]

SLE patients can theoretically develop ovarian failure due to autoimmune ovarian injury, altered hypothalamic–pituitary–ovarian axis, and diminished ovarian reserve,[4] current evidence suggests that they are as fertile as the general population.[5] Fertility preservation options should be discussed with patients prior to treatment. If the patient has a history of pregnancy, obstetric outcomes should be carefully reviewed, including history of fetal growth restriction (FGR), pregnancy-induced hypertension and preeclampsia, miscarriage, preterm birth, and intrauterine fetal death.In order to improve pregnancy outcomes in SLE patients, pregnancy should be well planned. Disease activity at the time of conception is an indicator of maternal outcomes, and high activity leads to poor outcomes.

With this background the study aimed to assess the effectiveness of pre-conceptional counselling in preventing adverse maternal and fetal outcomes among pregnant women with Systemic Lupus Erythematosus (SLE).

MATERIALS AND METHODS:

Present study is a prospective observational study conducted at MGMH Petlaburz, OMC tertiary care hospital from 01/06/2019 to 16/12/2021 (2 years 6 months). The study population were all women who were diagnosed with Systemic Lupus Erythematosus (SLE) and came for confirmation of pregnancy. During the study period 32 women were diagnosed with SLE and confirmed for pregnancy out of 40032 confirmed pregnancies inMGMH Petlaburz, OMC and included in the study. Among these cases most of them were referred from NIMS HOSPITAL which has a rheumatology department. Among these 32 women, 14 women have received pre-

conceptional counselling and remaining 18 women did not receive pre-conceptional counselling prospectively.
Informed consent from all study participants was taken before collecting data. Base line data like age, gravida and other investigations from medical case records were collected from all cases. Pre-conceptional counselling by gynaecologist, rheumatologist, nephrologist (During pre-conceptional counselling clients were educated about the disease, effect of disease on pregnancy, Disease activity was assessed, medication was reviewed, dosage of the drug was adjusted., pregnancy was planned during the phase of remission for 6 months).
All the pregnant women were followed up to 6 weeks after delivery. Maternal and fetal outcome was measured and compared in between women who received pre-conceptional counselling by gynaecologist, rheumatologist, nephrologist and women who did not receive pre-conceptional counselling. Maternal andfetal outcomes includes incidence of pre-eclampsia, lupus flare, fetal losses, Intra uterine Growth Restriction (IUGR), preterm labor, neonatal lupus and oligohydramnios.

Statistical analysis: Collected data was entered in Microsoft Excel and checked for completeness and missing values. Quantitative variables were presented in Mean and standard deviation and qualitative variables were presented in frequency and percentage. Chi-square or Fisher exact test was used to test the significant difference between two proportions. Odds ratio with 95% confidence intervals were calculated. P value less than 0.05 was considered as statistically significant. SPSS 26th version was used to calculate statistics.

RESULTS
Total of 32 SLE pregnancies were studied. The incidence of SLE in this hospital was 0.79 per 1000 pregnancies (32 out of 40032).
From table 1 it is observed that almost all the women belong to the reproductive age group and mean age was 23.7±4.2 years. Among these 17 (52.7%) of women were primigravida, 15 (45.5%) are multigravida out of which 7 (21.7%)with history of Bad obstetric history.
It is observed from the table 2 that among these 32 pregnant women, 16 (49.6%) were presented as lupus nephritis out of which 6 (18.6%)were grade 1 lupus, 5 (15.5%) were grade 3 lupus, 5 (15.5%) were grade 4 lupus nephritis. 3 (9.3%)cases have discoid rash, 2 (6.2%)cases have malar rash with repeated oral ulcers, 3 (9.3%) cases have refractory anemia for which evaluation was done, found to be AIHH, 3 (9.3%) cases have arthralgias, 5 (15.5%) of cases were associated with APLA syndrome out of which two were presented as arterial (right hemiplegia) venous (DVT) thrombosis and 1 case was associated with Sjogren's.Almost all patients were on multidrug regimens. T. azathioprine, HCQ, prednisolone, 2 (6.2%) also given cyclophosphamide therapy to control the disease, 7 (21.7%)were on high dose prednisolone 19 (52.7%)were on moderate and 6 (18.6%) were on low dose prednisolone Among these 32 cases 14 (43.7%)patients of women received pre-conceptional counselling and 18 (56.2%) patients did not receive pre-conceptional counselling.
From table 3 it is observed that among women who received PCC, 5 (35.7%) cases developed late onset pre-eclampsia without severe features, managed on inpatient basis, pregnancies were induced at 37 completed weeks which resulted in live births. Among women who did not receive PCC,9 (50%) cases developed pre-eclampsia. Among 9 cases with pre-eclampsia who did not

receive PCC,3 (35.7%) had developed early onset preeclampsia with severe features in which pregnancies terminated at 26-28 weeks for deteriorating maternal status, one case landed up in abruption IUD.Lupus flares were seen in 2cases only among PCC not received group, out of this 1case was terminated because detoriation in renal status of mother and lupus flare not seen in PCC received group. Another case is managed with high dose of steroids and terminated at 32-34 weeks of gestation and one case was received dialysis.9(50%) fetal wastages were noted in women who not received PCC compared to 3 (21.4%)women who received PCC. Among Women who received PCC, 3 (21.4%) cases were pre term labour and 3 (21.4%) cases were diagnosed as FGR and among women who did not receive PCC, 6 (33.3%) cases were pre term labour and 6 (33.3%) cases were diagnosed as FGR.

From Table 4 it is observed that among total 3 pregnancy losses in women who received PCC one case (33.3%) was spontaneously aborted in first trimester and 2 cases (66.7%) were terminated in 3rd trimester because of severe oligohydramnios with IUGR with uteroplacental insufficiency. Among 9 pregnancy losses in women who did not receive PCC 4 cases (44.4%) were 1st trimester losses, 3cases (33.3%) were second trimester pregnancy losses at 26-28 weeks because of severe pre-eclampsia. And 2 pregnancy losses in 3rd trimester one case was landed up in abruption IUD because of oligohydramnios with uteroplacental insufficiency and one case landed up in IUD because of Lupus flare. Neonatal lupus was not seen in both groups

Table1: Distribution according to demographic details of study population

Variable	**Number of patients (n=32)**	**Percentages**
Age intervals in years		
20-30	26	81.2
31-40	3	9.4
>41	3	9.4
Gravida		
Primigravida	17	53.2
Multigravida	15	46.8

Table2: Distribution according complications of SLE

Complications of SLE		**Number of patients (n=32)**	**Percentages**
Lupus nephritis (16)	Grade 1	6	18.6
	Grade 3	5	15.5
	Grade 4	5	15.5
Discoid rash		3	9.3
Malar Rash with repeated oral ulcers		2	6.2
Refractory anaemia (AIHH)		3	9.3
Arthralgias		3	9.3
APLA syndrome*		5	15.5

*Antiphospolipid antibody syndrome

Table3: Comparison of maternal and fetal outcomes between women who received PCC and not received PCC

Variable		Group		P value Odds ratio (95% CI)
		Received PCC* (n=14)	Not Received PCC (n=18)	
Pre-eclampsia	Yes	5 (35.7)	9 (50)	0.41
	No	9 (64.3)	9 (50)	0.71 (0.31-1.65)
Pregnancy outcome	Live birth	11 (78.6)	9 (50)	0.097
	Terminated	3 (21.4)	9 (50)	3.67 (0.75-17.73)
Pre term labour	Yes	3 (21.4)	6 (33.3)	0.457
	No	11 (78.6)	12 (66.7)	0.54 (0.11-2.72)
Fetal growth restriction (FGR)	Yes	3 (21.4)	6 (33.3)	0.457
	No	11 (78.6)	12 (66.7)	0.54 (0.11-2.72)

*Pre-Conceptional counselling

Table4: Distribution according to pregnancy loss

Variable		Group		P value
		Received PCC (n=3)	Not Received PCC (n=9)	
Pregnancy loss	1st trimester	1 (33.3)	4 (44.4)	0.301
	2nd trimester	0 (0)	3 (33.3)	
	3rd trimester	2 (66.7)	2 (22.3)	
Total		3 (100)	9 (100)	

DISCUSSION:

This study was conducted at tertiary care hospital is an observational study, 32 SLE pregnancies were included and divided into women who received PCC and women who did not received PCC. Maternal and fetal outcomes were measured and compared in both the groups. Women received PCC were treated with Tab. Ecospirin and in case of APLA positive cases inj. Heparin was started and fetal 2decho was done in antiRO, and antiL A positive cases, antepartum fetal surveillance was done till delivery.

The incidence of preeclampsia (50%) is comparatively increased in PCC not received group and it was early onset with severe features and pregnancies were terminated at 26-28 weeks, 1 case landed up in abruption. In PCC received group 35.7% were developed lateonset preeclampsia without severe features and case was managed after admission as per our hospital protocol, at 37 completed weeks pregnancies were induced resulted in live births.

Preeclampsia is a frequent complication in SLE pregnancies, it is difficult to differentiate pre eclampsia from lupus flare. In preeclampsia only proteinuria is seen and complement levels are usually normal or increased and thrombocytopenia, elevated serum levels of liver enzymes and uric acid are seen. Lupus nephritis, chronic HTN, APLA, chronic steroid use are the predisposing factors for pre-eclampsia in SLE.

Lupus flares were seen in 2 (11.1%) cases only in PCC not received group, out of this 1 case was terminated because detoriation in renal status of mother and no cases of lupus flare in PCC received group. Lupus flares can occur during all trimesters and in immediate postpartum period with equal frequency. In lupus flares proteinuria is seen with active urine sediment (red and white cells and casts), hypocomplementemia and increased titres of anti-DNA antibodies. Increased risk of flare is noted in women with active disease during conception in those who discontinued medication during pregnancy. Lupus flares may present as severe fatigue, arthritis, thrombocytopenia, deteorating renal status decreased complement levels, increased antids DNA titres. In this study it presented as fever, fatigue, deteorating renal status, low complement levels. Flares were managed with high doses of steroids.

50% of pregnancy losses were noted in PCC not received group when compared to 33.3% in PCC received group.P regnancy losses were more when women conceived during the active phase of disease associated with lupus nephritis Grade,3,4, hypocomplementemia, antiphospholipid antibodies, anti-DNA antibodies. Presence of antiphospholipid antibodies is the highest predictor of pregnancy losses. Anti-DNA antibodies may potentiate pregnancy loss by cross reacting with laminin, a protein critical for implantation.

Among Women who received PCC, 3 (21.4%) cases were pre term labour and 3 (21.4%) cases were diagnosed as IUGR and among women who did not receive PCC , 6 (33.3%) cases were pre term labour and 6 (33.3%) cases were diagnosed as fetal growth restriction(FGR). Preterm births are common in SLE and the presence of APLA, chronic HTN, disease activity increased risk of preterm birth. FGR is because of uteroplacental insufficiencies. Patients who received glucocorticoid therapy during pregnancy lead to FGR.

Neonatal lupus was not observed in both groups. Neonatal lupus is passively transferred autoimmune disease occurs in some babies born to mothers with anti-Rho/SSA and antiLa/SSB antibodies, it may present as skin rashes and complete heart block (2%). Neonatal lupus accounts for 90-95% of heart block cases in utero. Recurrence rate of CHB is 15% when the woman has given to complete heart block baby.

Based on a multi-centre analysis of 56 pregnancies of patients diagnosed with SLE before pregnancy, many agree that prognosis for both mother and child is best when SLE activity is in remission for at least 6 months before conception.[6] Compared with patients with clinically active SLE before conception, those in remission for at least 6 months before conception had a higher live birth rate (64% versus 88%), full-term delivery (64% versus 56%), and lower rate of exacerbation of SLE during pregnancy or postpartum (32% versus 28%).[7] In a retrospective analysis of 183 pregnancies in Korean females with SLE, based on a receiver operating characteristic curve for prediction of adverse pregnancy outcomes, Ko et al [8]stated that a stable period of at least 4 months is essential in reducing pregnancy loss, premature birth, pregnancy-induced hypertension, and FGR

When planning pregnancy, medication of the patient must be reviewed and adjusted to minimize its effect on the foetus while maintaining the current stable condition of the mother. Whether SLE activity is influenced by pregnancy has been a controversial subject for decades. It is generally considered that SLE flares are likely during pregnancy. However, some argue that SLE activity is worsened,[9] while others report that no change in disease activity is observed.[10] The mixed results are understandable, as the studies were mostly retrospective in design and patient history such as disease activity at the time of conception, previous history of disease, and

medication profile were diverse. In addition, different definitions were given for disease flare and, as described below, lupus flare during pregnancy is often difficult to distinguish from preeclampsia. Recently, attention is less on whether flare is likely or not and is more on which specific population of patients' needs special attention for exacerbation of SLE. Some argue that in patients with stable condition at the time of conception, disease activity is generally not worsened, and even if so, the flare is usually mild and seldom requires a change in the treatment.[11] A history of lupus nephritis and active disease at the time of conception are indicators of poor maternal outcomes.

Mothers should be assessed for disease activity once in each trimester or more frequently if they have active lupus. During first visit, after examination, RFT, CBC, Anti Ro, and Anti La antibodies, lupus auto coagulant, anti-cardiolipin antibody assay, anti dsDNA antibodies, complement levels (C3, C4), uric acid level has to be done, platelet count in each visit. Low dose aspirin, inj clexane must be started in APLA positive patients. Women with Anti Ro/La antibodies should undergo fetal monitoring for heart block. Fetal monitoring should be done weekly using (AFI, NST, biophysical score) in last trimester.If IUGR- umbilical artery doppler is recommended.

After observing the results, we can say that maternal and fetal outcome is much better in women who received pre-conceptional counselling. High disease index, chronic HTN, presence of APLA and lupus nephritis are the poor predictors which can be taken care of during pre-conceptional counselling. SLE women should plan to become pregnant when the disease should in remission for 6 months prior to pregnancy. this can be achieved by educating the patient about the disease, and explaining risks of adverse effects on mother and foetus and planning the Antenatal Care.

We can predict the better outcome if all SLE women receive pre-conceptional counselling which includes educating the patient about the disease and risk of adverse outcomes both for the baby and mother and the planning antenatal care.

With better treatment options and extensive clinical and molecular research, many SLE patients can have favourable pregnancy outcomes with careful management. Factors such as appropriate preconception counselling and medication adjustment, strict disease control prior to pregnancy, intensive surveillance during and after pregnancy by both the obstetrician and rheumatologist, and appropriate interventions, when necessary, play a key role.

CONCLUSIONS

It can be concluded from this study that SLE complicating pregnancies are considered as high-risk pregnancies which will adversely affect the maternal and neonatal outcome. Maternal and fetal outcome is much better in women who received pre-conceptional counselling. Pre-conceptional counselling decreases the adverse outcome of the disease to large extent, so every SLE diagnosed woman in the reproductive age group should be offered pre-conceptional counselling.

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