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SLE and Pregnancy

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting young individuals of child bearing age. Pregnancy is associated with an increased risk of lupus flares in 60% of the cases.[1] Pregnancy in SLE is categorized as high risk due to increased risk of spontaneous abortions, preeclampsia, intrauterine growth restriction (IUGR), intrauterine fetal death and preterm birth.[1] With the improvement in SLE survival rates due to medical advances, pregnancy outcomes have improved.[2] Management of pregnancy in lupus poses a challenge, both for patients and physicians.

PATHOGENESIS OF PREGNANCY COMPLICATIONS

Underlying chronic inflammation with associated autoantibodies and hormonal disturbances can affect pregnancy outcomes in SLE.[3] The increased incidence of miscarriages, IUGR, preterm birth and preeclampsia is the result of placental insufficiency with poor vascularisation and endothelial dysfunction. There will be an imbalance in production of angiogenic and antiangiogenic factors in maternal circulation tilting the balance towards antiangiogenic state. Excess use of glucocorticoids may increase vascular resistance in placental circulation by potentiating vasoconstriction.[3]

The increased rate of preterm birth in lupus can be due to stress, activating maternal or fetal hypothalamic pituitary axis. Stress will trigger labour by increased production of cortical and prostaglandins. The disease flare can induce preterm labour by increased production of cytokines, production and complement activation. Though oral prednisolone can reduce underlying inflammation, it is associated independently with preterm birth.[3]

Table 1: Contraindications to pregnancy

1. Severe pulmonary hypertension
2. Advanced cardiac failure
3. Severe restrictive lung disease
4. Moderate or severe chronic kidney disease (creatinine > 2.8 mg/dL)
5. Active lupus nephritis (proteinuria > 0.5g/day)
6. CNS disease in the past 6 months
7. Recent major thrombosis (< 2 years)
8. Current use of drugs like cyclophosphamide, mycophenolate mofetil, methotrexate, leflunomide, statins and angiotensin converting enzyme inhibitors

SLE DISEASE ACTIVITY IN PREGNANCY

Pregnancy probably increases the disease activity by 2-3 folds.[4] Mild to moderate flares are common. Severe flares are observed in 15-30 % of the cases. Cutaneous disease, arthritis and hematologic are the common forms of disease flare.[4] Lupus flares are observed throughout pregnancy and in post partum period. Lower rates of flares are observed in 3rd trimester due to lower estrogen levels and blunting of IL-6 levels.[5] The main risk factor for increased disease activity is presence of active disease 6 months prior to conception. Others include multiple flares in years before conception and discontinuation of hydroxychloroquine.[4]

Lupus patients have higher rate of comorbidities and complications than healthy women like hypertension, pre-gestational diabetes, renal impairment, pulmonary hypertension, major infections, thrombotic events, anaemia, antepartum haemorrhage, postpartum haemorrhage and thrombocytopenia.[6] There is 20 fold increased in the risk of maternal mortality.[6] Patients with evidence of irreversible organ damage prior to pregnancy are more likely to prone for medical and obstetric complication including worsening of previous organ damage. Patients with active lupus nephritis are associated with maternal hypertension, preeclampsia and preterm births. Hence it is advisable to plan pregnancy 6 months following renal remission and if possible to 12-18 months. Interstitial pulmonary disease may get worsened during pregnancy due thoracic compression by the growing uterus. Women with cardiac disease are at risk of cardiac failure due to volume overload.[1] The following table 1 summarises contraindications to pregnancy in SLE.[1]

IMPACT OF LUPUS ON PREGNANCY OUTCOMES

Women with SLE are at increased risk of miscarriages. The risk factors identified for miscarriages include hypertension, proteinuria > 500mg/day, thrombocytopenia and secondary antiphospholipid antibody syndrome (APS). Lupus patients have increased risk of preeclampsia by 3 to 4 fold. It is very difficult to differentiate preeclampsia from a flare of lupus due to common overlapping features like hypertension, raising proteinuria, oedema, renal function impairment and thrombocytopenia. Some of the features to differentiate preeclampsia from lupus flare are summarised in Table

Table 2: Distinguishing lupus disease activity from Preeclampsia

	Pre-eclampsia	Lupus flare
Hypertension	Usually present	May be present
24 hour urine protein	Does not differentiate	Does not differentiate
Onset of proteinuria	Abrupt, after 20 weeks	Abrupt or gradual, anytime
Casts in urine	Absent	Present in lupus nephritis
RBCs in urine	Absent	Present in lupus nephritis
Symptoms of active SLE, eg: Skin and joint involvement	Absent	Present
Seizures	Present in eclampsia	Present if there is neurological involvement
Uric acid	Elevated	Not elevated unless CKD
Urine calcium	low	Normal
Serum albumin	Low	Very low if nephritic syndrome
Liver function tests	May be affected (in HELLP syndrome)	Rarely affected in a flare of SLE
Complements (C3 and C4)	Unchanged from baseline in early pregnancy	Low (or lower from the baseline; complement levels increase in pregnancy)
Anti-dsDNA	Unchanged	Elevated

Abbreviations: CKD-chronic kidney disease, HELLP- hemolysis, elevated liver enzymes, and low platelets, SLE-systemic lupus erythematosus, RBC-red blood cell

Table 3: Factors associated with adverse maternal and fetal outcomes

Clinical factors	1. Active disease within 6 months prior to conception and during pregnancy 2. Active lupus nephritis or chronic kidney disease (creatinine > 2.8 mg/dL) 3. Maternal hypertension 4. Previous fetal loss
Serological factors	1. Antiphospholipid antibodies 2. Anti-dsDNA antibodies
Biochemical factors	1. Low complements 2. Proteinuria 3. Thrombocytopenia

2.[6,7]

Neonatal lupus syndromes (NNLS)

It refers to spectrum of clinical manifestations like cutaneous, cardiac, liver and systemic abnormalities observed in newborn infants born to mothers with Ro/SS-A and La/SS-B antibodies. Cutaneous neonatal lupus is the most common form of NNLS followed by cardiac and liver forms. Rarely hematologic, neurologic and splenic abnormalities are also noted. However these syndromes are usually benign and self limited within 6 months, once the maternal antibodies get cleared from baby's circulation.[1,6,7] Congenital heart block (CHB) is the most severe form of NNLS occurring in 2% of babies born to lupus mothers with positive anti-Ro/SS-A and anti-La/SS-B antibodies. The risk gets increased to 15-20% if the mother has already a child with CHB.[8] It is the end result of fibrosis of fetal atriovententricular node and myocardium due to transfer of anti-Ro/SS-A and anti-La/SS-B antibodies triggering immune mediated inflammation. Less frequent cardiac manifestations include cardiomyopathy and endomyocardial fibroelastosis.[6]

Several risk factors associated with adverse maternal and fetal outcomes were identified in multiple studies with varied population and are shown in Table 3.

ANTIPHOSPHOLIPID ANTIBODIES IN PREGNANCY

Antiphospholipid antibodies are identified in 20-55% of SLE cases. One quarter of the patients fulfil criteria for APS. The presence of antiphospholipid antibodies and APS is associated with increased risk of pregnancy losses and preeclampsia. Anticoagulation and antiplatelets forms the main stay of treatment.[9] Other newer options include intravenous immunoglobulins (IVIG), plasmapheresis and B cell depletion therapy.[10]

MEDICATIONS DURING PREGNANCY AND BREAST FEEDING

As a part of pre-pregnancy counselling, each lupus patient needs to be discussed about the use of appropriate drugs during pregnancy and breast feeding. Retrospective case series and isolated case reports form the basis for the use of medications during pregnancy and lactation. Table 4 summarizes the list of drugs commonly used in rheumatology practice and their impact on pregnancy and breast feeding.[1,7,2]

Table 4: Drugs commonly used in lupus patients and their effect on pregnancy and breast feeding

Drug	Recommendation for pregnancy planning	Effect on fetus	FDA classification	Recommendations for use in pregnancy	Breast feeding
NSAIDS	Avoided	Premature closure of ductus arteriosus, renal impairment, oligohydromnios	B in 1st and 2nd trimester D in third trimester	Avoid in 3rd trimester	Allowed
Prednisone and Prednisolone	Try to minimise the dose	Cleft lip, low birth weight, premature birth	B	Use lowest doses possible	Allowed (if > 40 mg wait for 3 hours)
Hydoxychloroquine	Continue to prevent lupus flares	None	C	Continue to prevent lupus flares	Allowed
Azathioprine	Need not be stopped	None	D	Used for lupus flares as an immunosuppressant and steroid sparing agent	Allowed
Methotrexate	Stop 3-6 months prior to conception	Aminopterin syndrome	X	No use in pregnancy	Not allowed
Leflunomide	Stop 2 years prior to conception	Malformations of head, vertebral column and limb defects	X	No use in pregnancy	Not allowed
Cyclophosphamide	Stop > 6 months	CY Clophosphamide embyopathy	D	Use only if no other options in case of life threatening maternal disease after 1st trimester	Not allowed
Mycophenolate mofetil	Stop 3 months prior to conception	Congenital anomalies especially ear	D	Use only if no other options	Not allowed
Rituximab	-	None	C	Attempt to discontinue 2 months prior to delivery if possible to prevent neonatal B cell depression	Allowed
IV IG	-	None	C	Used as needed	Allowed
Cyclosporine and tacrolimus	-	None	C	Can be continued	Probably safe
Aspirin	-	None	B/C	Used in obstetric APS	Allowed
Warfarin	Stop at conception	Warfarin embyopathy	X	Avoided especially in 1st trimester	Allowed
Heparin	-	None	C	LMWH is preferred due to ease of administration, high antithrombotic to anticoagulant ratio and predictable bioavailability	allowed

FDA-Food AND Drug Administration, LMWH- low molecular weight heparin, IV IG-intravenous immunoglobulins

Table 5: Baseline evaluation and monitoring of lupus patients at pregnancy

Pre-pregnancy	Every 6-8 weeks
1. Complete blood count 2. Prothrombin time and Partial thromboplastin time 3. Urine analysis-microscopy, 24 hour urine protein and creatinine clearance, spot protein/creatinine ratio 4. Lupus anticoagulant, anticardiolipin antibodies IgG and IgM, anti-β2 glycoprotein 1 IgG and IgM 5. Anti-Ro/SS-A, anti-La/SS-B, anti-dsDNA 6. Complements-C3,C4 7. Uric acid, AST,ALT, creatinine, blood glucose	1. Complete blood count 2. Urine analysis-microscopy, spot protein/creatinine ratio 3. Anti-dsDNA 4. Complements- C3, C4 5. Uric acid, AST, ALT, creatinine, blood glucose

CONTRACEPTION IN SLE

Every lupus patient need to be counselled on contraceptive practices as planned pregnancy is associated with good maternal and obstetric outcomes. The main contraceptive methods available to lupus patients include barrier methods, progesterone only pills and intrauterine devices (IUD). Barrier methods are highly unreliable. Though estrogen containing contraceptives are commonly used by general female populations, with the main concern about increased flares and thrombotic tendency, they are better avoided in cases of unstable lupus and those with APS. IUD either copper containing or progesterone IUD are safe and effective.[7,11]

MANAGEMENT

Management of SLE in a pregnancy requires multidisciplinary effort by rheumatologists, obstetricians and nephrologists when necessary. Obstetrician visits are scheduled every monthly till 20 weeks, then fortnightly till 28 weeks and thereafter every weekly. Rheumatologist visits are scheduled every 4-6 weeks and the frequency of visits can be increased in case of active disease.[2] Baseline evaluation is performed by history, physical examination and laboratory evaluation. The lists of investigations advised at baseline are summarized in table 5. Ultrasound and Colour Doppler aid in evaluation of fetal growth and amniotic fluid are carried out every monthly after 24 weeks. Fetal surveillance tests including the nonstress test (NST), the biophysical profile (BPP), and fetal umbilical artery Doppler velocimetry help in monitoring of IUGR. The testing begins usually at 26 weeks and there after every weekly until birth. Uterine artery evaluation is planned at 24 weeks and helps as a screening tool for preeclampsia.[7] Screening for CHB should start from 16 weeks and carried out every weekly. Fetal M mode echocardiography as a screening test helps in early diagnosis of CHB.[12]

SLE should be well controlled with low risk medications at lowest possible doses. Hydoxychloroquine should be continued throughout pregnancy as it decreases the number of flares, hypertensive disorders, preterm delivery rates and IUGR.[13] Hydoxychloroquine may also be helpful in prevention of CHB. Currently there is no definite treatment for established CHB. Fluorinated steroids (betamethasone and dexamethasone) may improve fetal survival in cases with myocarditis, hydrops or incomplete heart block. IVIG was studied in two open label interventional studies and it did not prevent or reduce the recurrence rate of CHB.[14]

Lupus flare during pregnancy can be managed by nonfluorinated corticosteroids like prednisone and prednisolone. The dose of steroids is guided by the severity and organ involvement. Usually lowest possible doses are recommended. Fluorinated glucocorticoids are recommended for fetal treatment (fetal lung maturation, prevention of CHB etc). There is no role for prophylactic steroids for prevention of disease flare.[1] For management of arthritis or serositis, NSAIDS can be used in lower doses for shorter time. NSAIDS are discontinued in 3rd trimester. Azathioprine and calcineurine inhibitors can be used when required as an immunosupressants and steroid sparing agents. IVIG and plasmapheresis are alternative options for uncontrolled flare.[2]

LUPUS NEPHRITIS

Management of lupus nephritis requires coordination of rheumatologist and nephrologist. Prednisolone forms the backbone of management. Hydoxychloroquine needs to be continued. Azathioprine is the preferred immunosuppressant. Cyclophosphamide can be used especially after 1st trimester in refractory cases. Emergency hemodialysis should be considered in case of rapidly deteriorating renal function.[12]

SUMMARY

Planning of pregnancy is optimal for key success in lupus with pregnancy. Lupus with pregnancy is a high risk condition with flares of the disease and poor pregnancy outcomes. It is challenging for rheumatologist and obstetrician to differentiate flare from preeclampsia. The SLE disease should be quiescent for at least 6 months for prevention of flares during pregnancy. With better maternal and fetal surveillance morbidity and mortality associated with lupus pregnancy has reduced.

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