Management of Pregnancy in Lupus Patients

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Abstract
Systemic lupus erythematosus (SLE) mostly affects young women of reproductive age group. SLE patients may conceive as any normal woman but complication may occur in these patients if the disease is active. Pregnancy in SLE may lead to 1. Aggravation of SLE (Lupus flare) 2. Pre-term delivery, intrauterine growth retardation and foetal loss (in presence of antiphospholipid antibodies) 3. Neonatal lupus especially in presence of Anti-Ro / La antibody. For a successful pregnancy, both from maternal and foetal aspects, disease should be quiescent for at least six months before the conception.

Lupus patients with pregnancy require specific management to improve the maternal and fetal outcomes. Many safe drugs are available for the management of pregnancy in SLE.

Introduction
SLE mostly affects young women of reproductive age group and fertility is not affected by SLE. Pregnancy in SLE may lead to 1. Aggravation of SLE (Lupus flare) 2. Pre-term delivery, intrauterine growth retardation and foetal loss especially in presence of antiphospholipid antibodies (APL) 3. Neonatal lupus especially in presence of Anti-Ro/ La antibody. For a successful pregnancy, both from maternal and foetal aspects, disease should be quiescent for at least six months before the conception.

Planning for Pregnancy
Lupus flare during pregnancy occurs more in patients with lupus nephritis (LN), active disease during the past six months before conception and discontinuation of hydroxychloroquine (HCQ). For a better outcome, drugs safe in pregnancy must be started preconception so that the disease remains under control.

Pregnancy should be contraindicated in following as maternal risk is considerably increased in these conditions:¹
1. Renal insufficiency (serum creatinine level >2.8 mg%)
2. Severe pulmonary hypertension (systemic pulmonary artery pressure >50 mmHg or symptomatic)
3. Severe restrictive lung disease (forced vital capacity <1 L)
4. Severe cardiac disease leading to heart failure

Complications of Pregnancy in SLE
Maternal and fetal risks are higher in lupus patients as compared to the healthy women. LN was associated with preterm birth and maternal hypertensive disorders in women with active, compared with quiescent disease.²

Disease Flares
If SLE is active at the time of conception then frequency of flare was found to be higher (61-67 %) during pregnancy as compared to those who were in remission for six months (7-33%).³ Patients with LN may have renal flare during pregnancy.⁴

Flares may occur with equal frequency in any of the trimester

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Table 2: Ante-natal monitoring by a rheumatologist and obstetrician (every 4-6 weeks and more frequently if the disease is active)

| Blood pressure monitoring (more frequent if there is history of hypertension, nephritis or pre-eclampsia) |
| Complete blood counts, Serum uric acid, serum urea, serum creatinine, liver function test |
| Complement C3, anti-dsDNA and urine examination, spot urine protein/creatinine ratio, Lupus anticoagulant (LA), anticardiolipin antibody (aCL) |
| USG monitoring for foetal growth and well being (between 16-20 weeks of gestation) |
| Fetal monitoring from week 26 AntiRo Antibody if positive – Fetal echocardiography weekly from week 16-26, then biweekly till delivery |
| Preeclampsia–Uterine artery Doppler (at week 20 and then 4 weekly), fetal umbilical artery Doppler velocimetry |

and in postpartum period. In SLE flare, photosensitive rash, oral or nasal ulcers, inflammatory arthritis, fever, lymphadenopathy, pleuritis, leucopenia, lymphopenia, immune haemolytic anaemia, thrombocytopaenia, active urinary sediment, proteinuria >300 mg/day, falling complement levels and rising anti ds-DNA levels, may be present. For these flares, patient may be given corticosteroid (CS) in lowest dose or short courses of high dose of CS and azathioprine or calcineurin inhibitors. Intra venous Immunoglobulins (IVIg) and plasmapheresis may be other options but fluid overload and risk of thrombosis may be seen with former.1

Maternal Morbidity

Pre-eclampsia, hypertension, bleeding, serious infections, preterm delivery, unplanned cesarean delivery, maternal venous thromboembolism occur with higher frequency in pregnant SLE patients.5

LN and pre-eclampsia may closely resemble as both may present with proteinuria, hypertension thrombocytopenia and deterioration in renal function.1 Some features can differentiate between these two conditions as enumerated in Table 3.1,6-8 Preeclampsia is a frequent complication of lupus pregnancy and occurs more frequently in LN.

Fetal Morbidity and Mortality

Higher rates of fetal loss, preterm birth (before 37 weeks), intra-uterine growth restriction (IUGR) and neonatal lupus syndromes are few of the complications which may be seen in foetuses born to SLE mothers. Active lupus, presence of nephritis, presence of APL, glucocorticoid use, hypertension, preeclampsia and thrombocytopenia increase the foetal complications.2-11 Umbilical artery Doppler ultrasonography should be done if IUGR is suspected.

Neonatal Lupus Syndrome (NLS)

Those lupus patients who have anti-Ro and anti-La subtypes of ANA targeting 52 kD or 60 kD SSA /Ro and 48 kD SSB/La proteins, respectively, cross the placenta and produce neonatal lupus syndrome (NLS), a passively acquired autoimmune syndrome. NLS is characterized by rash (photosensitive), haematologic (thrombocytopenia and neutropenia) and hepatic abnormalities or cardiac complications (Congenital heart block, endocardio-fibroelastosis, structural abnormalities and cardiomyopathy).12 Neonatal lupus rash manifests between 4–6 weeks after birth and may be seen up to 25% of newborns.13 These manifestations disappear 6-8 months after birth and coincide with the disappearance of the maternal antibodies.

Congenital Heart Block (CHB)

CHB affects about 2% of children born to primigravid women with anti-Ro antibodies.14 Risk of recurrence is high in anti Ro positive mothers with myx edema and risk also increases in subsequent pregnancies.15 Fetal genetic polymorphisms, involving the Fc-gamma receptors and transforming growth factor-β, and hypoxia have been suggested to have a role in CHB in NLS.16

CHB mostly develops between 18-24 weeks of gestation. Foetal echocardiography should be performed from 16-26 weeks of gestation and then biweekly. Foetal kinetocardiogram and transabdominal foetal electrocardiogram can diagnose these abnormalities.17,18 Increased PR interval (first degree heart block) forewarns the subsequent development of CHB. Since CHB is irreversible and mortality is high therefore all patients with increased PR interval should be promptly diagnosed and treated.19

Fluorinated corticosteroids (dexamethasone and...
betamethasone) cross placenta and reach foetal circulation and may normalize the increased PR interval but not in all as the effect is not consistently observed, so role of CS is controversial. Pacemakers may be required in the majority for better survival rates. To reduce risk of CHB in subsequent pregnancies, HCQ is effective. Role of IVIg in preventing this recurrence has not been found to be consistent.

Management of Pregnancy in SLE

Management of pregnancy in SLE patient requires co-efforts of rheumatologist and obstetrician.

Drugs for SLE Management During Pregnancy:

Drugs which are Safe in Pregnancy are:

HCQ: It is safe for fetus and should be continued during pregnancy as it leads to reduced disease activity, risk of CHB and neonatal lupus activity. Flare may occur on discontinuation of HCQ.

Azathioprine: This is safe during pregnancy in dose of 2mg/kg/day.

Tacrolimus and Cyclosporine: Since, both are safe during pregnancy and during breast feeding, these may be used for suppressing disease activity.

Anti-hypertensive drugs: Drugs safe in pregnancy are Methyldopa, Labetalol, Nifedipine, Hydralazine.

Acetaminophen: It is safe during pregnancy.

Heparin: It does not cross placenta and is safe during pregnancy. Ease of administration, higher anti-thrombotic to anti-coagulant ratio and predictable bioavailability makes low-molecular weight heparin (LMWH) the anti-coagulant of choice.

Anti-platelets: Aspirin is the only anti-platelet drug safe in pregnancy and may be continued if indicated.

Glucocorticoids: These must be used at the lowest dose (Prednisolone < 10 mg/day) that controls disease activity. High dose may be associated with diabetes mellitus, hypertension, preeclampsia and premature rupture of membranes. For disease flares short courses of high dose of CS or intravenous pulse therapy may be used. If patient has been on prolonged CS therapy stress dose of CS at the time of delivery may be required. Betamethasone and dexamethasone cross the placenta and is given in foetal heart blocks.

Calcium supplements, Vitamin D should be given to patients who are on corticosteroids and heparin as both these drugs can cause osteoporosis.

Drugs which are contraindicated:

1. **Cyclophosphamide**, Mycophenolate mofetil and Methotrexate: These should be discontinued 3 months before conception as all are teratogenic.
2. **Rituximab** (B cell depleting antibody) and Belimumab (BAFF inhibitor): Both should be discontinued before pregnancy as in Rituximab placental transfer may occur and for Belimumab data regarding safety are lacking.
3. Ticlopidine, Clopidogrel: All antiplatelets except Aspirin should be stopped before pregnancy.
4. **Warfarin**: It is teratogenic when used in early pregnancy. Warfarin may cross the placenta and cause fetal haemorrhage so it is better to avoid oral anti-coagulants.
5. **ACE inhibitors and ARBs**: These should be avoided in pregnancy as there is risk of ACE-inhibitor fetopathy, neonatal arterial hypotension, renal failure, and even death.
6. **Diuretics**: These may cause maternal volume depletion and reduced utero-placental perfusion.
7. **Bisphosphonates** should be discontinued 6-12 months prior to pregnancy.
8. **NSAIDs**: First trimester use may be associated with higher risk of congenital malformations. If used after 20 weeks of gestation foetal renal impairment may occur while use after 32 weeks of gestation can lead to premature closure of ductus arteriosus. However there are reports that NSAIDs are safe in first and second trimester of pregnancy.
9. **Leflunomide**: This drug should be discontinued 2 years before conception as it has a long half-life, or a wash out procedure must be undertaken with cholestyramine (or activated charcoal, 8 g three times a day) is given for eleven days and level of leflunomide in serum should be < 0.02 mg/L on two occasions 14 days apart before conception is contemplated). However, there are studies that inadvertent exposure to leflunomide did not lead to teratogenicity.
10. **Beta blockers**; All β blockers can cause IUGR and bradycardia in neonate and can lead to aggravation of Raynaud phenomenon in SLE.

Pregnancy with Antiphospholipid Antibodies (APL)

APLs are present in 25-50% patients of SLE but less than half of these patients have antiphospholipid syndrome (APS). APS may manifest clinically as thrombotic or obstetric complication along with one serological test Lupus anticoagulant (LAC), anticardiolipin antibodies (ACL) or Anti beta 2 glycoprotein 1, positive in medium to high titer on two occasions 12 weeks apart. APL positive patients present with 3 or more early pregnancy losses (<10 weeks) or one pregnancy loss >10 weeks or one premature birth due to severe pre-eclampsia or placental insufficiency. APLs increase the risk of pre-eclampsia, HELLP...
syndrome, placental insufficiency, IUGR and pre-term delivery. LAC is a better predictor of adverse pregnancy outcome as compared to other APL.11

The management of APL in pregnancy requires use of low dose aspirin and heparin.

In obstetric APS group aspirin and heparin significantly reduced the risk of pregnancy loss by 54%. With combination treatment live births of 74% were achieved compared to 58% with aspirin monotherapy. Heparin in addition to its anticoagulant effect and prevention of placental thrombosis, also blocks the activation of complement targeted to decidual tissues. Heparin also preserves trophoblastic function, reduces generation of inflammatory mediators and prevents obstetric complications. Heparin dose should be monitored by measuring activity of anti-factor Xa as prolonged activated partial thromboplastin time (aPTT) may be seen in these patients because of LAC.

Treatment of APS with Pregnancy

Use of LMWH except for its cost, is preferred over unfractionated heparin (UFH) because of their efficacy, less chances of bleed and heparin induced thrombocytopenia and osteoporosis. LMWH is replaced by UFH near term so that anti-coagulation may be reversed at the time of delivery.

APS without prior thrombosis: Prophylactic doses, such as 0.5 mg/kg/d of LMWH (enoxaparin) or 5000 u twice daily of UFH subcutaneously (SC) plus low-dose (81 mg) aspirin is recommended. Once or twice during treatment, anti-factor Xa activity should be checked, 4 hours after the last dose for a level of 0.2 to 0.6 U/mL.

APS with prior thrombosis: Full anticoagulant doses, such as 1 mg/kg every 12 hours or 1.5 mg/kg/day of enoxaparin or 10,000 to 12,000 units UFH SC every 12 hours may be used. Alternatively Dalteparin 100 units/kg SC every 12 hours or 200 units/kg/day may be used. Target anti-factor Xa 4 hours after the last dose for a level of 0.5 to 1.1 U/ml (with twice-daily dosing), or 1.0 to 2.0 U/ml (with once-daily dosing).

Treatment begins at conception and continues for 6 to 12 weeks postpartum if the patient has no history of thrombosis, and indefinitely if the patient has a history of thrombosis. Dosing will need to be reduced if renal impairment is present.

Patient refractory to low dose Aspirin (LDA) and heparin may be given corticosteroids, IVlg, and plasmapheresis though data are limited regarding efficacy of these drugs and modalities. Warfarin is contraindicated in pregnancy because of teratogenic effects.

Thrombocytopenia Complicating Lupus Pregnancy: Thrombocytopenia may be caused by active SLE, maternal APS, HELLP syndrome and pre-eclampsia. Late onset thrombocytopenia occurs in pregnant patients with APS and there is an increased risk of fetal injury. Heparin therapy may lead to heparin induced thrombocytopenia (HIT) but unless antibodies specifically associated with HIT are demonstrable, heparin should not be discontinued.

In APS patients severe thrombocytopenia (<50,000/mm³) requires IVlg, control of hypertension and early delivery.27

Breast Feeding

Short-acting NSAIDs, antimalarials, low-dose prednisone (less than 15 to 20 mg/day), warfarin and heparin are safe for the infant, as little or no active drug is secreted in breast milk. Pregnancy should be planned when the disease is quiescent for six months. Effective contraception should be adopted if the disease is active.

Preconception assessment should be done regarding renal status, organ involvement, APL and anti Ro antibody and treatment should be effectively instituted to make the disease quiescent.

Maternal complications like disease flares, pre-eclampsia, and foetal complications i.e. prematurity, IUGR and NLSs (including CHB) should be diagnosed and treated early.

Many safe drug options are available which should be started to improve maternal and foetal outcomes.

References


