SLE in Pregnancy

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Abstract:
Systemic lupus erythematosus is specially a disease of young women in their child bearing age . It has been found that SLE disease activity can repair in pregnancy even though patient is in complete remission state before the pregnancy. Besides this, pregnancy complications are higher in SLE patients. Another important issue is the use of drugs to control SLE because some of these drugs are potentially terotogenic. Fetal outcome is also a challenging issue. Therefore, multi-disciplinary approach has key role in the management of Lupus pregnancy.

Key words: Systemic lupus erythematosus (SLE), Lupus pregnancy, Lupus flare, Anti-phospholipid Antibody Syndrome, Neonatal Lupus Syndrome, Congenital heart block.

[BSMMU J 2010; 3(1): 54-59]

Introduction:
Systemic lupus erythematosus (SLE) is a chronic inflammatory disease with multisystem involvement in which the tissues are damaged by autoantibodies and immune complexes and primarily affects young female at childbearing age[1]. Pregnancy is an important matter in every woman's life. However, different maternal diseases can complicate pregnancy. One of them is SLE, which can turn the life miserable during pregnancy if it is not treated properly.

Epidemiology:
There is no standard statistical data in SLE for Bangladesh. Incidence and prevalence of SLE is still very low in India. A prevalence study in India (carried out in a rural population near Delhi) found a point prevalence of 3 per 100,000[2]. Sex specific SLE prevalence in the UK: Females: 49.6/100,000(ie 1 in 2000 adult women have SLE) and Males: 3.6/100,000. 90% of cases of SLE affects women, the incidence of SLE during the child bearing age being 1in 500. The fetal effects are mainly prematurity, intrauterine growth restriction, neonatal lupus, and in extreme cases stillbirth. Congenital heart blocks result as a consequence of diffuse myocarditis and fibrosis[1].

Diagnostic criteria
Patients who are antinuclear antibody (ANA) negative are very unlikely to have SLE[3]. However, a patient is classified of having SLE if any of 4 or more of following criteria met (Table-I)[4,5].

Revised ACR classification criteria for SLE (1997 update)[5].

Item	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminences, sparing nasolabial folds.
Discoid rash	Erythematous, raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions.
Photosensitivity	Skin rash as a result of unusual reaction to sunlight by history or on physical exam.
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
Non-erosive arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling or effusion
Pleuritis/pericarditis	a. Pleuritis- convincing h/o pleuritic pain or rub or pleural effusion on physical examination ORb.Pericarditis- documented by ECG, rub or effusion
Renal disorder	a. Persistent proteinuria > 0.5 gm/day or > +++, ORb. Cellular casts- may be red cell, Hb, granular, tubular or mixed

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Item	Definition
Neurological disorder	a. Seizures- in the absence of offending drugs, or known metabolic derangement, e.g. uraemia, ketoacidosis or electrolyte imbalance, ORb. Psychosis- in the absence of offending drugs, or known metabolic derangement, e.g. uraemia, ketoacidosis or electrolyte imbalance
Haematological	a. Haemolytic anaemia with reticulocytosis, OR b. Leukopaenia < 4000/cu mm on 2 or more occasions, ORc. Lymphocytopenia < 1500 on 2 or more occasions, ORd. Thrombocytopenia < 100,000/cu mm in the absence of offending drugs
Immunological disorder	a. Anti-DNA: antibody to native DNA in abnormal titre, OR b. Anti-Sm: presence of antibody to Sm nuclear antigen, ORc. Positive finding of aPL antibodies based on: 1) '! serum level of IgG or IgM aCL or 2) a positive test result for lupus anticoagulant, using a standard method, or 3) a false-positive test for syphilis for at least 6 months and confirmed by TPI or FTA-abs test
Positive ANA	An abnormal titre of ANA by immunofluorescence or an equivalent assay

Why SLE is important in pregnancy?

SLE is a disease condition, which is, not only hampers the normal life of a woman, but also can create a dangerous situation during pregnancy. Disease flare of SLE can occur during pregnancy. Pregnancy related complications are common with SLE. Fetal outcome is also poor. There is a increased risk of abortions (2-3 times), intrauterine growth retardation and stillbirth. Therefore, lupus pregnancy is labelled as 'high-risk' pregnancy.

SLE associated maternal diseases and complications:

SLE patients suffer from different kinds pregnancy related complication more frequently than non-SLE women do. Actually, there are two main problems; *firstly increased pregnancy related complication due to SLE* and secondly *SLE disease flares due to pregnancy.*

Common pregnancy related complications[1,2,6]:

- Pregnancy related hypertension
- Preeclamsia
- Eclamsia
- HELLP syndrome
- Ante-partum haemorrhage
- IUGR
- Pre-maturity, Abortion & Still birth
- Gestational diabetes (increased by prednisone used for SLE Rx)

Other maternal complications of lupus pregnancy:

- Infection
- Deep vein thrombosis
- Pulmonary embolism
- Cerebro-vascular accident (stroke)
- Pulmonary hypertension

Risk factors for Pre-eclampsia in SLE:

1. After 20 weeks usually in <35% pregnancies
2. First pregnancy
3. Pre-eclampsia in prior pregnancy
4. Twins or multifetal gestation
5. Steroids, especially >20mg/day prednisone
6. History of lupus nephritis &/or hypertension
7. History of anti-phospholipid antibody syndrome

What is Flare?

Flare may be defined as unpredictable bouts of the disease after a period of remission. A number of validated indices are available for quantifying disease activity or flare of SLE. Two of the indices, the "*Systemic Lupus Erythematosus Disease Activity Index"* (SLEDAI) and the "*British Isles Lupus Activity Group"* (BILAG), have been the predominant ones used for defining flare[7]. However, the "*Safety of Estrogen in Lupus: National Assessment*" (SELENA) investigations did not think these definitions of flare were sufficient, and devised new definitions to separate ''mild/ moderate'' flare from ''severe'' flare[7,8]. All these criteria, although some minor differences are present, describe the reappearance of SLE related symptoms and signs. It is important to follow a certain list of criteria for screening out of flare. However, clinicians' experiences is sometime more important than these prescribed list to detect the flare. The fatal complications of SLE flare are renal involvement and CNS manifestations.

Lupus flare in pregnancy: Why does it matter?

Lupus flares are very much common in pregnancy. It increases maternal morbidity, risk of premature delivery & fetal loss. Most important thing is therapeutic issues.

Drugs, needed for control of flare, are sometimes teratogenic.

SLE related fetal disease and complications:
Other than prematurity & fetal loss, neonatal lupus syndrome is another fetal complication. Causes of premature delivery are *poor intrauterine growth, reduced liquor, fetal distress, rupture of membranes, pre-eclampsia, spontaneous labour*. Risk factors for premature delivery are anti-phospholipid antibodies, active SLE at conception, SLE flare, renal disease, high blood pressure.

***Neonatal Lupus Syndrome*:**
Neonatal lupus syndrome is an unusual condition due to the passage of maternal antibodies (specially Anti-Ro/SS-A and Anti-La/SS-B) to unborn fetus. The main features are congenital heart block (CHB), transient cutaneous lupus lesions, Cytopenias, hepatic, and other systemic manifestations[9,10].

Antenatal care & Preconception counselling:
Same as normal non-SLE antenatal care; but more concentration should be given to identify early diseases flares; to search for SLE related pregnancy complications and regular monitoring of fetal conditions. Patients suffering from active disease, should be kept under special observation.

However, aims & objectives of normal non-SLE antenatal care are:

- To promote, protect and maintain the health of pregnant women
- To detect high risk cases and give them special attention
- To predict complications and prevent them
- To remove anxiety associated with pregnancy
- To reduce maternal and infant mortality and morbidity
- To teach elements of child care, nutrition, hygiene and sanitation
- To sensitize her regarding family planning
- To attend the under 5 children accompanying the mother

Preconception counselling & Planning for pregnancy:
Routine counselling of SLE patients with incomplete family should include emphasis on the need for planned pregnancy. The incidence of flare during pregnancy with conception while in remission is less than 10%. It is strongly recommended that the disease should be in clinical remission for at least 6 months before the patient plans for pregnancy. The best time for conception is after 6-12 months of remission with hydroxychloroquine but no cytotoxic drugs. At the onset of pregnancy, a complete assessment of disease activity and severity should be made. The spouse and other family members should be counselled[2]. Childbearing should not be contemplated in women with pulmonary hypertension and those with lupus nephritis with a baseline serum creatinine >250µmol/l[11].

Evaluation at first visit: Initial evaluation should be based on thorough history taking and physical examination along with careful BP measurement.

Investigations during first visit:

- Routine urine analysis
- Hb%, ESR, total WBC count, differential count and platelet count
- Serum creatinine
- 24 hour urinary total protein,(Creatinine clearance test if possible)
- Anti-ds-DNA (***raised level indicates active SLE or impending flare*[2].**)
- Anti-Ro(SS-A) and Anti-La(SS-B), Anti-Phospholipid Antibodies (Anti cardoilipin Ab & Lupus anticoagulant).
- Serum C3 &C4 level (***low C3 indicates active SLE or impending flare in over 80% of patients*[2].**)
- Fasting blood glucose if at high risk
- serum lipids if patient is nephrotic or on steroids
- Coombs' test
- Ultrasound examination(Should be selective rather than routine)
- Others: Hepatitis B & C serology, Anti HIV screening, Syphilis serology (as a part of normal antenatal checkup)

Follow up at subsequent visits: History and clinical examinations should be focused on identification of disease flares and pregnancy related complications.

Laboratory assessment includes:

- Blood counts including platelet, Hb%, ESR
- Routine urine analysis
- Serum creatinine, Urinary protein:creatinine ratio
- FBG/Modified OGTT 24 to 28 weeks
- anti-dsDNA and C3 {At the end of each trimester}
- Biophysical profile (BPP) scoring from 28 weeks
- Women detected to have either anti-Ro or anti-La antibodies should be offered serial foetal echocardiograms between 16-24 weeks of gestation[11].

General principles of treatment of lupus pregnancy:
Treatment principle of SLE is an integrated management protocol to maintain good health, prevent complications and early detection & rapid treatment of flares. For doing all these, counselling of patient and her family members is very much important. Patient should know what the danger signs are.

General advice:
Avoiding sun exposure is very important to prevent flares. Mother should take low salt diet containing adequate amount of vitamins and minerals.

Treatment when there is no sign of flares or complications:

Drugs those can be used safely during pregnancy

1. Folic acid (this is recommended)
2. Hydroxychloroquine
3. Low dose Aspirin(75mg/d) if Antiphospholipid antibodies present, in high risk patient or presence of nephritis for prevention of pre-eclampsia,

There are ***many controversies of using steroid*** in this group of patient to prevent flares as flare prophylaxis. Use of steroid increases the risk of fetal cleft palate, IUGR, PROM, DM, pre-eclamsia.

Treatment for Lupus flares:
Lupus flares should be treated with the appropriate steroid (usually prednisolone) dose. Azathioprine and cyclosporine can be used in pregnancy with active SLE. Cytotoxic drugs such as cyclophosphamide should be avoided during first trimester except in rare circumstances such as pulmonary alveolar haemorrhage or class IV nephritis due to SLE[2]. These drugs have some side effects over pregnancy and fetus. Cyclophosphamide & Methotrexate are the most teratogenic among them and should be avoided in pregnancy. More safety data are needed for the use of mycophenolate mofetil. Some adverse effect of drugs on pregnancy has been descried in the following table-II.

Anti-phospholipid Antibody Syndrome (APS):
If antiphospholipid syndrome is present, there is greatly increased risk of thrombosis and foetal loss. Warfarin must be stopped as early as possible after conception (preferably the next day of her first mense is missed and pregnancy confirmed) and daily subcutaneous injections of low molecular weight heparin or low dose of heparin sodium along wih low dose aspirin must be continued until delivery. The heparin is omitted 12 hours before delivery or caesarean section whereas low dose aspirin may be continued. After post partum bleeding stops, usually within a week after delivery, warfarin is restarted. Corticosteroids are not recommended for APS alone because they increase maternal morbidity. In refractory cases, intravenous immunoglobulin (IVIG) can be tried[2]. Abortion and fetal loss is very much common in APS. Immunotherapy with IVIG that contains anti-idiotypes directed towards patients pathogenic antiphospholipid antibodies has been tried to prevent pregnancy loss in different centre[20].

Table-II
Adverse effects of drugs

Drugs	Toxicity in pregnancy
Prednisolone	Increased risk of Cleft lip[12], cleft palate[12], premature rupture of membrane, hypertension[6], preeclampsia, DM
Azathioprine	Found to be safe in therapeutic dose in different studies[13,14]. However, some clinicians believe it causes bone marrow suppression both in mother and fetus. It has been found to be teratogenic in mice and rabbits.
Cyclosporine	Found to be safe in therapeutic dose in different studies[15]. The most important problem faced in the newborn whose mother is treated by cyclosporine is the severe intrauterine growth retardation, reported by Pickrell et al[16].
Cyclophosphamide	Crosses the placenta and can cause fetal toxicity when administered to pregnant women. Abnormalities (missing fingers and/or toes, cardiac defects, hernias) have occurred in infants born to women treated with the drug during the pregnancy. Other complications like haemorrhagic cystitis, bone marrow suppression, infection etc may complicate pregnancy[17,18].
MTX	Potentially teratogenic. It causes neural tube defect[19].

Anti-Ro or Anti-La antibodies positive women:

When incomplete heart block is detected in utero (detected by fetal doppler) , corticosteroids that cross the placenta (dexamethasone or betamethasone) need to be administered to the mother in order to decrease inflammation in the fetal heart and prevent progression to complete heart block[11,21]. Plasmapheresis and IVIG are also tried for prevention of CHB. (Successful prevention)

Issue of medical termination of pregnancy:

Issue of termination of pregnancy depends upon certain factors. These are pregnancy outcome and maternal condition. Therefore, obstetrician should consider some questions like *"Is there any chance of fetal complications that can lead to delivery of unsurvival or handicap baby*" or *"Is there any possibility of endanger mother's life if pregnancy continue"*. Teratogenic effects of SLE drugs (specially MTX & Cyclophosphamide) can raise former question. That is why; women should not be pregnant while on these kind of drugs and proper counselling is needed to the patients who are taking these drugs regarding their fetal outcome. But even then, when a mother get pregnant during the treatment of SLE with MTX or Cyclophosphamide, should be offered diagnostic tests with a view to early detection of teratogenicity, like- Chorionic villus sampling, Amniocentesis, Cordocentesis, 3-D ultrasound, Fetal MRI; which one is suitable for age of gestational period. If the laboratory analysis shows that the fetal condition is untreatable or associated with significant handicap then patient may be suggested for termination of pregnancy. Alternatively, the time, place and mode of delivery may be planned in order to ensure the optimal prognosis of neonate.

Delivery:

Women who have required glucocorticoids (e.g., prednisone) to control systemic lupus erythematosus during pregnancy need an increased dose, called ***a stress dose***, during delivery[22]. The increased dose helps the body respond normally to the physical stresses of childbirth. Delivery should be done in such hospital where paediatric care is available; if possible in a hospital where Neonatal ICU is available. Indication of caesarean section same as normal pregnancy. Indications for Caesarian section include maternal reasons (avascular necrosis of the hips with inadequate hip abduction) or foetal reasons (foetal distress, abnormal nonstress test, cephalo-pelvic disproportion and transverse presentation etc.).

Neonatal care:

After delivery heart rate of the baby should be counted and also there should be a search for any cutaneous lesion. Treatment of established congenital heart block (CHB) is difficult[23]. Therefore, it is better to prevent during pregnancy as mentioned earlier. Most of the time cutaneous lesion can be treated with topical steroids.

Puerperium:

During the postpartum period, the mother should be watched for infection and disease exacerbation; both require aggressive treatment, when detected. In Anti-phospholipid antibody Syndrome, warfarin is restarted after bleeding stops.

Issues of Breast-feeding:

Majority of drugs are excreted in human milk in variable amounts. From neonatal perspective, maternal intake of prednisolone less than or up to 30 mg/day, warfarin, cyclosporine in standard doses and weekly chloroquine for malaria prophylaxis are considered safe. If the dose of prednisolone is greater than 30 mg/day, feeding should be avoided for 4 hours after ingestion of the morning dose of steroid. By this time the blood levels are quite low and very limited amounts are secreted into the milk. However, breastfeeding is contraindicated if mother is on cyclophosphamide, azathioprine, hydroxychloroquine for SLE.

Advice of contraception:

Barrier methods are the safest method for contraception. However, low dose estogen or progesterone only pills are relatively safe. High dose estrogen containing pill should be avoided. OCP should be avoided in antiphospholipid syndrome, other thromboembolic diseases, highly active disease, migraine, Raynaud's phenomenon. Use of intrauterine devices is controversial because it causes infections like endometritis, PID etc.

Conclusion:

SLE is a multisystem disease. Therefore, interdisciplinary approach is needed to treat the disease. Doctor, patient and her family should work together for planning of pregnancy and during pregnancy to overcome the complications.

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