Systemic lupus erythematosus and pregnancy: Today’s scenario
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Citation

Abstract
Systemic Lupus Erythematosus (SLE) is a rare disease, but the fact to be well appreciated is that 90% of the patients are females, that too of the reproductive age. Years ago, all medical texts said that lupus patients could not have children, and if they became pregnant, they should have therapeutic abortions but the scenario has changed today. The consensus is, in the absence of active disease, renal failure, cyclophosphamide treatment, or treatment with high dose steroids, patients with SLE should be as fertile as the general population and should not be discouraged from being pregnant. The pregnancy, though, should be managed as a high risk pregnancy. Frequent antenatal visits and timely investigations to predict disease activity are the gold standards of care.

INTRODUCTION
Systemic Lupus Erythematosus (SLE) is an autoimmune disease, characterized by damage to multiple organ systems by autoantibodies and immune complexes. Though the disease is rare, overall incidence being 5-100 per 100,000 populations; but the fact to be well appreciated is that 90% of the patients are females, that too of the reproductive age. That is the reason that fertility and pregnancy become major issues while dealing with a patient of SLE.

Years ago, all medical texts said that lupus patients could not have children, and if they became pregnant, they should have therapeutic abortions, but the scenario has changed today. It has been documented that currently 50% of all lupus pregnancies are completely normal, and 25% deliver normal babies prematurely. Fetal loss due to spontaneous abortion or death of the baby, accounts for the remaining 25%. So, while not all of the problems of pregnancy with lupus have been solved, pregnancies are possible, unlike thought in the past.

EFFECTS OF SLE ON PREGNANCY
Fertility of patients with SLE is usually unaltered by the disease. Pregnancy rate of 2.0 to 2.4 pregnancies per patient has been described, not only during disease remission but also during periods of disease activity. However, certain factors like active disease, high dose corticosteroids and immunosuppressive treatment cause anovulation and thus might contribute to a lower fertility rate in some patients. So, the consensus is, in the absence of active disease, renal failure, cyclophosphamide treatment, or treatment with high dose steroids, patients with SLE should be as fertile as the general population and should not be discouraged from being pregnant. The pregnancy, though, should be managed as a high risk pregnancy. Frequent antenatal visits and timely investigations to predict disease activity are the gold standards of care.

Neither all pregnancies with SLE will have complications nor all babies will have problems and actually fetal outcome can be predicted. In the absence of active disease, lupus nephritis, secondary antiphospholipid antibody (APLA) syndrome, anti Ro and anti La antibodies and high dose steroid therapy, a fairly good fetal outcome can be prognosticated.

Anti Ro and anti La are the only antibodies in SLE that can cross the placenta and only 1% of infants with positive maternal autoantibodies, get affected with neonatal lupus erythematosus (NLE). NLE is a syndrome with cardiac, dermatologic, hepatic, hematologic manifestations alone or in combination. Cardiac manifestations of NLE are most scary. Anti Ro antibodies block the calcium channels in the fetal cardiac musculature, causing conduction defects. That is the reason behind cardiac rhythm abnormalities and complete heart block is the hallmark of NLE. Cutaneous
lesions are predominantly seen in the scalp, face, and neck which can be present at birth or may develop later, at times after exposure to sun light. These lesions are transient. Eruptions usually disappear when maternal antibodies are absent in the neonatal circulation at about sixth month of life. Risk of recurrence of NLE in future pregnancies is approximately 25%.

**EFFECT OF PREGNANCY ON SLE**

Whether the frequency of flares increases in pregnancy or not, is a field of controversy. However it is a well known fact now, that even if the flares are more frequent, they are not more serious as compared to flares in a non pregnant state. These flares can precipitate at any trimester or even during the postpartum period.

Despite the inconsistency of results generated, a common agreement is that lupus flares during pregnancy are fairly common, with a frequency of more than 57%. Every patient with SLE should therefore be followed up during pregnancy under the assumption that there is a risk of flare.

**PLAN OF PREGNANCY**

Before planning for a pregnancy patient should be well aware of the course of disease, complications during pregnancy, and about the probability of effects on the fetus and the neonate. She should be informed about the need of more frequent antenatal visits, approximate cost of the investigations during the course of pregnancy and also about the chances of flare up and its treatment.

The pre-pregnancy visit aims at assessment of the activity of lupus, organ damage, laboratory tests, and medication exposure. Pregnancy should be best undertaken during periods of quiescent disease. Nephritis, if present, should be in remission for at least 6 months. Renal remission means stabilization of renal functions, no sediment abnormalities, proteinuria of less than 1 g/day and normal compliment (C3/C4) levels. Pregnancy with lupus nephritis even inactive, should be handled as a very high risk pregnancy.

**MONITORING LUPUS PREGNANCY**

When a SLE patient presents with amenorrhea, transvaginal sonography (TVS) is the investigation of choice for confirmation of pregnancy, as urine pregnancy test (UPT) may be falsely positive. In one study false positive UPT occurred in 14 of 140 (10%) non-pregnant lupus patients, including one male.

Antenatal visits have to be more frequent, fortnightly in first and second trimesters, then weekly in third trimester. History and physically examination should be done as for any other antenatal woman. As the symptoms and signs of SLE are nonspecific and so much overlap is there in the physiological changes in pregnancy and the symptomatology of SLE that investigations become the main means of monitoring pregnancy.

The battery of investigations that is recommended for the first visit comprise - complete blood count (CBC) including platelets, urinalysis, creatinine clearance; anticardiolipin antibody (ACA), lupus anticoagulant (LA), anti β2 glycoprotein one to rule out secondary antiphospholipid antibody (APLA) syndrome; anti ds DNA, compliment (C3, C4, CH50) levels to know the disease activity; anti Ro, anti La antibodies to predict the fetal affection and glycosylated hemoglobin, if patient is on steroids, to know the glucose control in preceding months.

Platelet count should be repeated every month because of high risk of thrombocytopenia in lupus pregnancies. For SLE patients with renal involvement, every month creatinine clearance and 24 h urine protein should be checked.

Otherwise (if no renal involvement), creatinine clearance and 24h urine protein can be done on trimester basis. Other investigations that have to be repeated in each trimester are compliment levels (C3, C4, CH50) and anti ds DNA, to keep an eye on the disease activity and predict the flare.

Antinuclear antibody (ANA) once has come positive, is not required to repeat, neither in the course of pregnancy nor otherwise.

As far as fetal surveillance is considered after confirmation of pregnancy by TVS, anomaly scan is done as for a normal pregnancy, at around18-20 weeks. If mother is positive for anti-Ro, anti La antibodies then only fetal ECHO cardiography is indicated which should be performed at 22-24 weeks of gestation. As these fetuses are more at risk of IUGR fetal sonography for growth monitoring is recommended every 4 weeks, starting at 18-20 weeks. Fetal surveillance should also be performed routinely 30-32 weeks onward.

**FIELDS OF POTENTIAL MISTAKES**

SLE flare / normal pregnancy: Anemia can be a manifestation of either of the two. While in SLE flare anemia is expected to be hemolytic, in normal pregnancy anemia is because of hemodilution and thus normocytic
normochromic. Thrombocytopenia is a common manifestation of SLE and mild thrombocytopenia (with platelet counts between 100,000 and 150,000/mL) is found in 8% of normal healthy pregnant women too. SLE presents with pain of small joints especially of hand and wrist, while the more common bony aches in pregnancy are related to pelvic girdle and lumber spine. But at times when arthralgia is generalized it becomes a diagnostic sphinx. Though in both SLE and pregnancy skin lesion involves the malar area specifically but it should be kept in mind that chloasma of pregnancy is only a discoloration without erythema, erosion or scaling; unlike the SLE rash. The high estrogen levels of pregnancy increase the proportion of hairs in the anagen (growing) phase; however, when this effect reverses postpartum, there is increased hair loss as a greater proportion of hair follicles enter the telogen (resting) phase. Similarly hair loss can also be a manifestation of SLE flare. In both the conditions ESR will be raised.

To sort out the conundrum between a SLE flare and physiological change in pregnancy anti ds DNA, compliment levels and C-reactive protein (CRP) are of great help.

Lupus nephritis / pre eclampsia: Both conditions may cause hypertension, proteinuria, and worsening renal function. Some clinical clues might help as anti ds-DNA will be raised while compliment levels (C3, C4, CH50) will be low in case of lupus nephritis. In preeclampsia proteinuria will be there, whereas in lupus nephritis with protein, active urinary sediments (red blood cell cast, granular cast, epithelial casts) are also present. Disease activity in other organs points towards lupus nephritis. While patient with SLE nephritis will show good response with steroids, preeclampsia will get worsened. Though neither required nor done practically, the gold standard to differentiate these two conditions is renal biopsy.

SAFETY OF MEDICATION IN LUPUS PREGNANCY

Glucocorticoids have been well studied and although they have been associated with cleft lip in rabbits, this finding has never been confirmed in humans. Glucocorticoids, such as prednisone and hydrocortisone, are inactivated in the placenta by 11 beta-dehydrogenase and have little effect on the fetus and thus are drugs of choice during pregnancy. Dexamethasone and betamethasone, however, have been shown to cross the placenta in an unmetabolized form and thus should not be used unless there is an intention to treat the fetus. However it should still be kept in mind when using prednisolone for prolonged periods in pregnancy that there is risk of PROM, IUGR, gestational diabetes mellitus (GDM) and hypertension.

NSAIDs can be associated with premature closure of the ductus arteriosus in the third trimester, and this complication may lead to primary pulmonary hypertension in the newborn. There have been reports of excessive neonatal bleeding as a result of platelet dysfunction secondary to high doses of aspirin taken shortly before delivery. NSAIDs also can cause oligohydramnios, presumably owing to fetal oliguria. If needed only paracetamol is recommended for analgesia.

No report of hydroxychloroquine (HCQ) causing fetal problems has been described in the literature so far. On the contrary there is good evidence that withdrawal of HCQ may precipitate flare, thus its discontinuation is not advocated in pregnancy.

Regarding immunosuppressants as far as possible it should not be used in pregnancy. However for patients with severe lupus where immunosuppresion becomes must, azathioprine can be used, with risks explained. Cyclophosphamide is teratogenic in humans and methotrexate is lethal for the fetus.

MANAGEMENT OF FLARES DURING PREGNANCY

Flares are to be managed more aggressively. Mild to moderate exacerbation without neurological and renal involvement can be treated with initiation or increase in the dose of oral prednisolone (15-30 mg/day). For severe exacerbation without neurological or renal involvement, doses of 1.0 to 1.5 mg/kg/day should be used. Exacerbations involving nervous system or kidney are treated with intravenous (IV) pulse glucocorticoid approach, in which IV methylprednisolone is given at 10-30 mg/kg for 3-6 days, followed by 1.0-1.5 mg/kg/day prednisolone in divided doses. In all cases, after the crisis is over glucocorticoids should be tapered over the course of one month, to a maintenance dose of 5-10 mg/day.

DELIVERY MANAGEMENT

As far as mode of delivery is considered vaginal birth is not contraindicated in lupus pregnancy. Cesarean section is done only for other obstetric indications. Exacerbation can occur during labor. Regardless, stress dose of glucocorticoids should be given during labor or cesarean, to all patients who have been treated with chronic steroids within the previous
year. Hydrocortisone, in three doses of 100 mg, 8 hourly IV is an acceptable regimen. Continuous fetal heart monitoring and presence of the pediatrician at the time of delivery is must. Obstetrician attending the delivery should always be prepared for postpartum hemorrhage, due to thrombocytopenia.

**MANAGEMENT OF PUERPERIUM**

Theoretically under the protective effect of progesterone during the course of pregnancy the chances of flares are less but as soon as the delivery occur this protective effect vane off with the drop in plasma progesterone levels. For this reason puerperium should never be ignored. Prompt recognition and proper management of flare can be life saving. For obvious reasons these patients are more prone to develop postpartum hemorrhage, puerperal sepsis and thromboembolism.

**BREAST FEEDING**

Breast feeding is not contraindicated per se. However there can be insufficient milk production. Moreover at times rashes might make breast feeding painful. In this scenario breast milk suppression is advised and for the neonate formula feeds can be initiated. If the mother is on steroids, adjustment of feeding with steroid therapy, is recommended.

**CONTRACEPTION**

Though patients with lupus are not discouraged from having children simultaneously they should not be encouraged to become pregnant, too many times and too frequently. For spacing intra uterine devices (IUDs) can not be given for the fear of infection because of immune dysregulation, nor can the high dose estrogen for the scare of flare, but still low dose oral pills can be recommended. Progesterone only contraceptive methods and barrier methods are the other options. If permanent contraception is sought vasectomy is a better choice, as the stress of surgery may again precipitate flair during tubectomy.

**CONCLUSION**

Patients with SLE have normal fertility. In the absence of renal failure, cyclophosphamide treatment, active disease, or treatment with high dose steroid, patients with SLE should not be discouraged from being pregnant, although they should be informed of the increased risk of pregnancy complications and fetal wastage. Frequent antenatal visits and timely investigations to predict disease activity are the gold standards of care.

**References**
