

# Systemic Lupus Erythematosus and Pregnancy

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Systemic lupus erythematosus (SLE) predominantly afflicts young women. The current availability of effective treatment regimens has meant that many patients achieve remission which can be long lasting. In this context, it is only rational that pregnancy becomes an important issue for the lupus patients and their care givers. Indeed, a high proportion of lupus patients, with expert care, can look forward to a successful pregnancy.<sup>1</sup> This paper reviews the current concepts regarding SLE and pregnancy under two major headings (1) Effect of pregnancy on SLE and (2) Effect of SLE on pregnancy.

## Effect of Pregnancy on SLE

The effect of pregnancy on maternal disease is controversial. While some studies report exacerbation of SLE during pregnancy<sup>1,2</sup> others have not reported increased flares.<sup>3,4</sup> The only study on this aspect of SLE from our country did not report a flare-up of disease during pregnancy.<sup>5</sup> The clinician should be alive to the fact that assessment of lupus activity during pregnancy can be difficult. Physiological changes like alopecia, palmar erythema; increased glomerular filtration rate leading to increase in proteinuria etc. are liable to be misconstrued as flares of the disease by the unwary.<sup>6</sup>

Notwithstanding the varying reports available in literature, most rheumatologists agree that lupus flares are frequent in pregnancy with a flare rate of 0.06-0.136 per patient-month. Lupus may flare during any trimester or post-partum necessitating close follow up. The flares are generally mild with arthritis and cutaneous manifestations.<sup>7</sup> Patients with pre-existing major organ involvement like kidneys need monitoring for renal flare. Flares are managed by escalation of treatment like nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Major organ flares (like renal disease) may need institution dose escalation of azathioprine. Cyclophosphamide is contraindicated in pregnancy. Prophylactic corticosteroids to prevent lupus flares during pregnancy are not recommended.<sup>4</sup>

## Effect of SLE on pregnancy

### a. Fertility

In general, SLE does not affect the fertility of patients. Pregnancy rates of 2.0-2.4 pregnancies per patient have been described.<sup>7</sup> The fertility may be adversely affected in a small subset of patients with renal failure, cyclophosphamide treatment, and anovulatory cycles due to active disease or high dose corticosteroids. So far as preservation of gonadal function is concerned intravenous pulse cyclophosphamide given intermittently is better than daily oral cyclophosphamide. The chances of permanent amenorrhea are higher with the latter. Two

approaches have been suggested in an attempt to preserve fertility in lupus patients undergoing cyclophosphamide treatment:<sup>8</sup> (a) use of oral contraceptives to put the ovary to rest, and (b) use of gonadotrophin releasing factor.

Infertile women with lupus can be considered for in-vitro fertilization (IVF). Oestrogens given as part of IVF regimens may exacerbate SLE. However, most flares are manageable and the current consensus is not to deny this treatment option to selected patients.<sup>9</sup>

### b. When and how to time pregnancy

Planned pregnancies are a better option in lupus patients. Pregnancy should be undertaken at a time when the disease has been in remission for at least 6 months. Patients need to be counseled about various contraceptive options. Barrier contraception (condom, diaphragm etc.) is the safest contraceptive method in SLE.<sup>8</sup> Intra-uterine devices like copper-T which carry an increased risk of infection, especially in women on immunosuppressives, are best avoided. The currently available oral pills with very low dose of oestrogens are probably safe in SLE patients with one exception, namely patients with antiphospholipid syndrome. Most authorities believe that reports of SLE exacerbation with oral pills in the older literature were due to higher dose of oestrogens used. A large trial, Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA), is currently underway in United States to address these issues. Progesterone only pills or depot progestogens are safe in lupus although side effects like menstrual irregularities, spotting, weight gain may adversely affect patient acceptance. Women who have completed their families can safely undergo tubal ligation.

### c. Obstetric issues during pregnancy

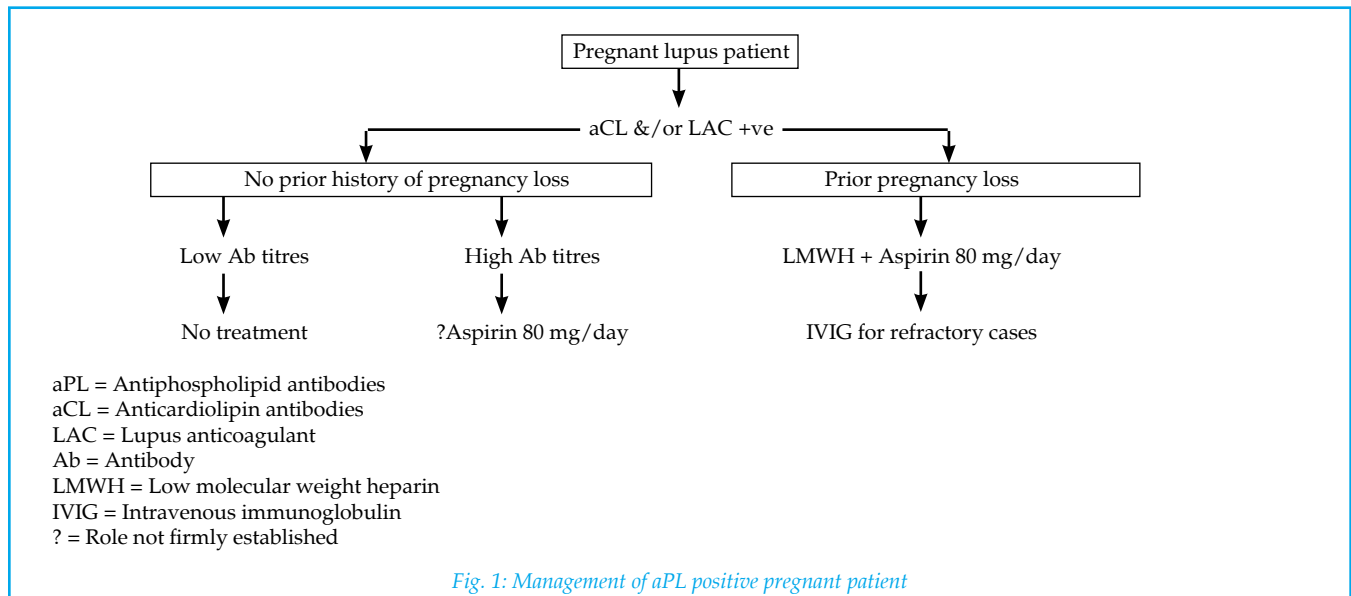
Lupus patients have an increased risk of pre-eclampsia (5-38%) as compared to women without SLE.<sup>7</sup> Risk factor for pre-eclampsia include pre-existing hypertension, nephritis and presence of antiphospholipid antibodies (aPL). Clinical, differentiation between pre-eclampsia and renal flare is difficult because both conditions lead to hypertension, proteinuria, oedema and deterioration in renal function. Table 1 lists some of the helpful differentiating features between these conditions. Pre-eclampsia and renal lupus may coexist in the same patient. The treatment principles for pre-eclampsia and eclampsia are the same as in the non-lupus patient.

### d. Foetal issues

The foetal outcome in lupus pregnancy is complicated by a higher rate of abortions (6-35%), still-births (0-22%), prematurity and intra-uterine growth retardation (IUGR). The predictive factors for foetal wastage include active lupus nephritis, previous history of foetal death and the

**Table I : Differences between, pre-eclampsia and exacerbation of renal lupus in a patient with SLE**

	Pre-eclampsia	Renal flare
C3/C4 levels	Increased	Decreased
Anti-dsDNA titres	Unchanged	Increased
Urine sediment	Usually benign	Active
Response to steroids	Worsening	Improvement



presence of aPL.<sup>10</sup> Maternal hypertension and high dose steroids are predictors for prematurity and IUGR. High dose corticosteroids can also lead to premature rupture of membranes. Foetal loss related to the antiphospholipid syndrome usually occurs in the second and third trimesters. Both lupus anticoagulant and anti-cardiolipin antibodies (aCL) are associated with foetal loss. The current approach to APS is summarised in Figure 1. Corticosteroids are currently not advocated for the pregnancy losses due to APS unless there are associated autoimmune problems.

#### Neonatal lupus erythematosus (NLE)

NLE is defined by the presence of<sup>11</sup> (a) maternal antibodies to the 52 kD SSA/Ro, 60 kD SSA/Ro or 48 kD SSB/La ribonucleoproteins, and (b) complete heart block (CHB) or transient skin rash. Most manifestations of NLE are transient. The antibodies usually clear over a few weeks. CHB, the most common manifestation of the NLE syndrome, is permanent and carries significant mortality and morbidity to the offspring.<sup>12</sup> Occasionally, the mother may be totally asymptomatic and the detection, of complete heart block in the infant draws attention to the presence of anti-Ro/anti-La antibodies in the mother. SLE per se is not a risk factor for the development of CHB, which depends solely on the presence of anti-SSA/Ro or anti-SSB/La ( $\approx 7\%$  in anti-Ro/SSA antibody positive mothers).<sup>7'</sup>

The exact pathogenesis of foetal CHB is not known. The placental transfer of maternal autoantibodies in the second trimester could be responsible. Foetal echocardiography during 16-24 weeks of gestation can help detect CHB in utero. Maternal dexamethasone or betamethasone (which cross the placenta), IVIG and plasmapheresis are some of the

modalities which have been tried. However, the results are disappointing.

Lupus patients often ask their doctors about the chances of their children getting SLE. Lupus is a multigenic disorder. The familial occurrence is low ( $\approx 10\%$ ).<sup>13</sup> Many of the affected family members have only serologic abnormalities. Lupus patients, thus, run a very low risk of their offspring developing SLE in later life.

#### Medications and Breast feeding in lupus pregnancy

High dose aspirin and NSAIDs are avoided in the last few weeks of pregnancy because of their effects on uterine contraction, platelet function, and premature closure of ductus arteriosus. Prednisolone is safe in pregnancy since it does not cross the placental barrier and is the corticosteroid preparation of choice for use in the pregnant lupus patient. In cases of CHB steroids which cross the placental barrier like betamethasone, dexamethasone are preferred. High dose corticosteroids carry the risk of IUGR, premature membrane rupture, gestational diabetes, hypertension, osteoporosis etc. Hydroxychloroquine is safe in pregnancy and lupus patient who becomes pregnant should continue taking hydroxychloroquine.<sup>15</sup> Chloroquine, however, has been reported to cause congenital anomalies. Cyclophosphamide is teratogenic and contraindicated in pregnancy. Lupus patients who need cytotoxic agents in addition to corticosteroids e.g. lupus nephritis, can be safely put on azathioprine.<sup>15</sup> Cyclosporine A is reserved for patients with severe disease activity during pregnancy.

NSAIDs with a short half-life (ibuprofen, etc.), are preferred in nursing mothers. NSAIDs are contraindicated in nursing mothers with jaundiced infants because of the fear of kernicterus. Large doses of aspirin, because of fear of salicylate

### Box I : Pregnancy and SLE -- Key points

- SLE may flare at any time during pregnancy. All lupus pregnancies to be considered high risk and monitored closely
- Fertility rates in lupus patients similar to general population
- Pregnancy best undertaken when disease is quiescent
- Increased incidence of pre-eclampsia, miscarriage, prematurity and intra-uterine growth retardation.
- All lupus patients intending to become pregnant to be screened for anti-Ro and anti-La antibodies
- Hydroxychloroquine, NSAIDs, prednisolone, azathioprine can be continued during pregnancy if the condition of mother's SLE so warrants.
- Prednisolone and hydroxychloroquine compatible with breast-feeding. Breast-feeding contraindicated in nursing mothers on azathioprine, cyclophosphamide, methotrexate, cyclosporine A.

intoxication are best avoided. Nursing mothers can continue to take prednisolone and hydroxychloroquine. Cytotoxics such as methotrexate, azathioprine, cyclophosphamide and cyclosporine A are contraindicated in breast feeding mothers.

### CONCLUSIONS

Better management and multidisciplinary care have meant that successful pregnancies are becoming the rule rather than exception in SLE. All lupus pregnancies should be considered high risk and closely monitored. Patient education is crucial for a successful pregnancy outcome.

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