

# LUPUS AND PREGNANCY

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Women with systemic lupus erythematosus (SLE) have complicated pregnancies; one-third will result in a cesarean section, one-third will have preterm birth, and more than 20% will be complicated by preeclampsia. When compared with other women, SLE patients are at increased risk for maternal death, preeclampsia, preterm labor, thrombosis, infection, and hematologic complications during pregnancy. Close monitoring by multidisciplinary team approach, which includes rheumatologist, obstetrician and nephrologist, is needed in view of elevated risks.

Many features of lupus can be mimicked in normal pregnancy state as a result of physiological changes in pregnancy. These include melasma, preeclampsia, and increase circulating blood volume. Hence pregnancy is appropriately labeled as lupus mimicker.<sup>1,2</sup> Preparation for pregnancy which includes fertility and contraception, pregnancy management and good pregnancy outcome have to be addressed.

## EFFECTS OF LUPUS ON FERTILITY

Fertility is normal in lupus patients, unless there has been prolonged exposure to cyclophosphamide. Timing pregnancy to coincide with a period of SLE quiescence is important.

### Fertility Preservation on Cyclophosphamide Therapy<sup>3</sup>

Intravenous cyclophosphamide therapy (IVC) remains an important therapy for patients with severe SLE including lupus nephritis (LN). With IVC therapy there are multiple risks like premature ovarian failure with sterility, menopausal symptoms, increased long-term risks of osteoporosis and coronary artery disease that may delay young women with SLE from undertaking IVC therapy, despite the risks of poor long-term renal outcome.

Cyclophosphamide causes injury to rapidly dividing granulosa cells that normally provide hormonal support to developing follicles and oocytes. Another theory is that oocytes, both in resting and developing stages arrested in meiosis are more vulnerable to damage.

Strategies to prevent ovarian toxicity from cyclophosphamide focuses on preventing ovulation, decreasing ovarian metabolic activity and blood flow, hence cyclophosphamide dose to the ovary. Gonadotrophic Releasing Hormone agonist (GnRHa) suppresses pituitary release of gonadotrophins, thereby creating a temporary 'prepubertal' state. GnRH agonist Leuprolide depot in dose of 3.75 mg/month can be administered subcutaneously with monthly IVC. General risks from GnRHa include menopausal symptoms, thrombosis and ovarian hyperstimulation.

Egg, embryo, or ovarian cryopreservation techniques remain potential options for women on cyclophosphamide seeking to preserve reproductive potential.

Alternative therapies include fortnightly 500 mg of IVC over 3 months followed by azathioprine maintenance as in Euro-lupus Nephritis Trial it has shown similar efficacy to the 2-year NIH regimen.

## PRE-PREGNANCY EVALUATION

### Check List to Be Addressed Prior To Pregnancy in SLE Patient.

- Any previous pregnancy?

**Table 1: Pregnancy complications in SLE**

First trimester (1-12 weeks)	Spontaneous abortions recurrent miscarriages
Second trimester (after 20 weeks)	Antepartum hemorrhage Preeclampsia Eclampsia
Third trimester (24-38weeks)	Preeclampsia eclampsia
Labour and postpartum period	Preterm labour Caesarian section Postpartum hemorrhage

- Previous pregnancy complications?
- SLE organ involvement
- Degree of irreversible damage
- Recent or current SLE activity?
- Presence of anti-phospholipid antibodies/syndrome?
- Positivity of anti-Ro/anti-La?
- Current treatment: any 'forbidden' drugs?

#### **Pregnancy Should Be Avoided In SLE Patients With**

- Severe pulmonary hypertension (estimated systolic PAP >50 mmHg or symptomatic)
- Severe restrictive lung disease (FVC < 1 liter)
- Heart failure
- Chronic renal failure (Cr >2.8 mg dl)
- Previous severe pre-eclampsia or HELLP despite therapy with aspirin and heparin
- Stroke within the previous six months
- Severe lupus flare within the previous six months

#### **PREGNANCY COMPLICATIONS IN SLE**

Pregnancy of SLE patients can be complicated by a number of obstetric and neonatal problems.<sup>4,5</sup> Besides an increased rate of pregnancy losses the most frequent fetal complications observed are premature birth, intrauterine growth restriction (IUGR), premature rupture of membrane and precocious premature rupture of membrane, while preeclampsia/eclampsia seems to be the most frequent obstetric complication

#### **Feto-Maternal complications**

Throughout pregnancy there is an increased risk of thrombotic events like stroke, deep vein thrombosis and pulmonary embolism; various infections including sepsis and pneumonia; and hematological complications viz. anaemia and thrombocytopenia. Other complications are listed in Table 1.

#### **Pregnancy losses**

Overall, about 20% of pregnancies to women with SLE end

**Table 2: Differentiation between lupus nephritis and preeclampsia**

	<b>Lupus nephritis</b>	<b>Preeclampsia</b>
Timing in pregnancy	Any time	After 30 weeks gestation
First pregnancy	No impact	Increased risk
Preeclampsia in prior pregnancy	No impact	Increased risk
Active urine sediment	Positive	Negative
Complement (C3 & C4)	Low	Normal
Anti-dsDNA antibody	Positive	Negative
Serum uric acid	No change	>5.5 mg/dl
Urine calcium	Normal	< 195 mg/24 hrs
Treatment	Immunosuppression	Termination of pregnancy if near term

with spontaneous abortion or stillbirth. Lupus activity and antiphospholipid syndrome (APS) are the two most important risk factors for increased pregnancy loss. Previous pregnancy loss, proteinuria, thrombocytopenia, and hypertension in the first trimester are each independent risk factor for pregnancy loss. A woman with any of these risk factors has a 30% to 40% chance of suffering a pregnancy loss.<sup>6,7</sup>

#### **Preeclampsia**

Women at particular risk for preeclampsia include those having first pregnancy, history of preeclampsia or renal disease, active SLE at conception, positive anti-double-stranded DNA antibody (dsDNA) or anti-ribonucleoprotein antibodies, low complement levels, obesity, and hypertension. Patients with preeclampsia and convulsions qualify definition for eclampsia, which warrants for immediate termination of pregnancy. Differentiation of preeclampsia from LN is highlighted in Table 2.

#### **Prematurity Preterm Birth & Low birth weight**

Risk factors for preterm birth include lupus activity before and during pregnancy, higher prednisone dose, and hypertension. There is suggested role of inflammation of chorioamniotic membrane which causes preterm labour. SLE has a primary effect on intrauterine fetal growth, irrespective of activity of the disease at any gestational age. The birth-weight for the SLE patient's baby is lower.

#### **MEDICAL COMPLICATIONS**

There is increased risk of medical complications which include pre-gestational diabetes mellitus, hypertension, pulmonary hypertension, renal failure and thrombophilia in SLE patients.

#### **Antiphospholipid antibody syndrome**

The antiphospholipid antibodies are the major risk factor for pregnancy loss in patients with SLE. It causes significant morbidities with respect to maternal thrombosis, fetal growth retardation, infertility and recurrent miscarriage syndrome.<sup>8</sup>

Treatment includes low-dose Aspirin, started preconception (at time of diagnosis) plus Inj. Heparin, 5000 units subcutaneously every 12 hours or Inj. Dalteparin, 5000 units subcutaneously every 24 hours immediately post-conception along with aspirin; both continued till term.

The postpartum period is actually the greatest risk period for the mother in terms of thrombosis. Hence, heparin should be continued for 6 weeks after delivery.

### Neonatal Lupus (NL)

Maternal anti-SSA/Ro and/or anti-SSB/La autoantibodies lead to NL approximately in 2% of exposed offspring which results in cardiac disease.

Cardiac manifestations of NL include conduction abnormalities (first, second or third-degree heart block) and life-threatening cardiomyopathy. Because of the inability of cardiac tissue to regenerate transient passive exposure to acquired antibodies explains irreversible nature of conduction defects. Until recently only high grade AV block could be diagnosed prenatally but tissue velocity-based fetal kinetocardiogram (FKCG) enables accurate measurement of AV conduction time and diagnosis of low-grade AVB.<sup>9</sup>

PRIDE study evaluated role in early diagnosis and treatment during pregnancy of anti-Ro antibody exposed fetuses.<sup>10</sup> Two aims of PRIDE study (PR Interval and Dexamethasone Evaluation) were mechanical PR interval, defined using the gated-pulsed Doppler technique and the efficacy of dexamethasone. The conclusion of this study was that first-degree block is no more common than third-degree block but, unlike the latter, may be reversible with dexamethasone in rare cases. In a study comprised of eight pregnancies in mothers with anti-SSA/Ro antibodies and a previous child with CHB, treatment with 1 gm/kg of IVIG at the 14th and 18th week of gestation prevented CHB in seven cases. IVIG may be particularly effective in prevention of the passively acquired autoimmune disease of CHB.<sup>11</sup>

The recurrence of CHB in a subsequent pregnancy appears to be unaffected by maternal health and antibody status, by the use of steroids or by fetal gender or death of the previous child with CHB.

The classical description of cutaneous NL comprises of annular or elliptical lesions on the face, scalp, trunk, or extremities. The rash appears most often by 6 weeks postpartum and disappears generally without any sequelae by 6 months coincident with the clearance of maternal antibodies from the child's circulation. Biopsy reveals basal cell damage with a dermal mononuclear infiltrate

### Lupus Flares

The influence of pregnancy on disease activity in women with SLE is variable. The risk of lupus flare is increased drastically

if the woman has had active lupus in the 6 months before pregnancy and discontinuation of Hydroxychloroquine.

SLEPDAI ("P" stands for pregnancy) and LAI have been validated in SLE pregnant patients showing a sensitivity of 93% and a specificity of 98% and are one of activity instruments used in clinical studies of lupus flares. The only two systems that emerged as more significant in pregnancy were renal and hematologic.

Skin, joint, and constitutional symptoms are most commonly encountered. Arthralgias are common among pregnant women because of increased weight as well as the effect of relaxin on the joints.

### Renal Flare

Patients who have never had renal disease or in complete remission i.e. normal creatinine and no proteinuria, before pregnancy are unlikely to develop active renal disease simply due to being pregnant even in presence of anti-ds-DNA antibodies. However, Patients remain at increase risk of flare in months after delivery. In patients starting pregnancy with moderate renal failure (serum creatinine  $\geq 1.4$  mg/dL), there is a greater decline in renal function compared to non-pregnant patients. For those patients receiving immunosuppressive therapy for their lupus nephritis, pregnancy does not appear to accelerate their disease progression.<sup>12</sup>

Many similarities are shared between preeclampsia versus lupus nephritis like high blood pressure, proteinuria and pedal edema; however it is important to differentiate between the two as their management differs (Table 2).<sup>1</sup>

### Hematological flare

In pregnancy there is disproportionate increase in blood volume and hematocrit hence anemia being common in 50% pregnancy. Hemolytic anemia and thrombocytopenia could occur due to lupus flare or HELLP syndrome. Hematologic disease, in particular thrombocytopenia, is also common during pregnancy, with the risk ranging from 10% to 40% in different cohorts.

## MONITORING OF LUPUS PREGNANCY

Table 3 lists the monitoring of pregnancy in lupus to achieve good pregnancy outcomes.

## DRUG IN PREGNANT LUPUS PATIENTS

Hydroxychloroquine has been proven to decrease the risk of SLE flare, improve the prognosis of SLE nephritis, and prevent death. It is also very well tolerated with arguably the best side-effect profile of any medication available to treat SLE. There is an increased risk of flares on discontinuation of HCQS in pregnancy. Azathioprine may be the safest immunosuppressant medication taken during pregnancy. The fetal liver does not have the enzyme required to metabolize

**Table 3: Monitoring pregnancy in lupus**

Trimester	Labs	Maternal monitoring	Fetal monitoring
First trimester	CBC with differential platelets, creatinine function tests, glucose, albumin, urine analysis, urine protein/creatinine ratio, C3, C4, CH50, anti-dsDNA, antinuclear antibody, lupus anticoagulant, anti-SSA and SSB antibody	Hypertension and renal monitoring Lupus disease activity Index assessment Echocardiogram (optional)	Routine USG
Monthly thereafter	visits CBC with differential platelets, creatinine function tests, glucose, albumin, urine analysis, urine protein/creatinine ratio, C3, C4, CH50, anti-dsDNA, antinuclear antibody	Hypertension and renal monitoring Lupus disease activity Index assessment	First fetal echo at 16 weeks Fetal Echo every 1-2 weeks after 16 weeks Biophysical profile

azathioprine into its active form. However commencement of azathioprine in the mid-pregnancy for a lupus flare may be risky, as there is increase in pregnancy loss as shown in Hopkins lupus pregnancy cohort.

Another option for treatment mid-pregnancy lupus flare is intravenous immunoglobulin (IVIg). IVIg can be particularly helpful in controlling hematologic and renal disease. Table 4 depicts common drugs and their effects on pregnancy.

### CONTRACEPTION

At the time of conception SLE should be under good control, and the patient should be taking only allowed medications.<sup>13</sup> This highlights the use contraception during periods of moderate to highly active lupus. Options are available include OC depot progesterone and IUCD.

Risks with estrogen component include increased risk of SLE flares and thrombosis. Depot-progesterone offers convenience, with the need of only quarterly injections, and less breakthrough bleeding as compared to oral progestones.

Woman with SLE who has a single partner and who is not on immunosuppressive drugs other than low-dose prednisone is considered an appropriate candidate for IUCD.

**Table 4: Common drugs and their effects on pregnancy**

Drug	In pregnancy	Adverse Effects
Corticosteroids	Less than 20 mg	Multifactorial diseases Cleft palate
NSAIDS		Constriction of ductus
Hydroxychloroquine	Yes, decrease flares	Not at recommended doses
Azathioprine	Safe	-
Cyclophosphamide	Contraindicated	Chromosomal abnormalities, IUFD
Mycophenolate mofetil	Contraindicated	Reports of malformation of corpus callosum and digits
TNF inhibitors	Uncertain	possible association of VATER syndrome
Cyclosporine	Can be used with azathioprine	Growth restriction

### REFERENCES

1. Clowse ME. Lupus activity in pregnancy. *Rheum Dis Clin North Am* 2007; 33:237-52.
2. Buyon JP. Updates on lupus and pregnancy. *Bull NYU Hosp Jt Dis* 2009; 67:271-5.
3. Mersereau J, Dooley MA. Gonadal failure with cyclophosphamide therapy for lupus nephritis: advances in fertility preservation. *Rheum Dis Clin North Am* 2010; 36:99-108.
4. Petri M. The Hopkins Lupus Pregnancy Center: ten key issues in management. *Rheum Dis Clin North Am* 2007; 33:227-35.
5. Frank R, Witter, MD. Management of the high-risk lupus pregnant patient. *Rheum Dis Clin N Am* 2007; 33:253-265.
6. Doria A, Tincani A, Lockshin M. Challenges of lupus pregnancies. *Rheumatology (Oxford)* 2008; 47(Suppl 3):iii9-12.
7. Ambrósio P, Lermann R, Cordeiro A, et al. Lupus and Pregnancy—15 Years of Experience in a Tertiary Center. *Clin Reviews Allergy Immunol* 2010; 38:77-81.
8. Bick RL. Antiphospholipid Syndrome in Pregnancy. *Hematol Oncol Clin N Am* 2008; 22:107-120.
9. Izmirly PM, Llanos C, Lee LA, et al. Cutaneous manifestations of neonatal lupus and risk of subsequent congenital heart block. *Arthritis Rheum* 2010; 62:1153-7.
10. Friedman DM, Kim MY, Copel JA, et al; PRIDE Investigators. Utility of cardiac monitoring in fetuses at risk for congenital heart block: the PR Interval and Dexamethasone Evaluation (PRIDE) prospective study. *Circulation* 2008; 117:485-93.
11. Rein AJ, Mevorach D, Perles Z, et al. Early diagnosis and treatment of atrioventricular block in the fetus exposed to maternal anti-SSA/Ro-SSB/La antibodies: a prospective, observational, fetal kinetocardiogram-based study. *Circulation* 2009; 119:1867-72.
12. Wagner SJ, Craici I, Reed D, et al. Maternal and foetal outcomes in pregnant patients with active lupus nephritis. *Lupus* 2009; 18:342-7.
13. Duarte C, Inês L. Oral contraceptives and systemic lupus erythematosus: what should we advise to our patients? *Acta Rheumatol* 2010; 35:133-40.