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## Systemic lupus erythematosus and pregnancy – a challenge to the clinician

### Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune connective tissue disorder that predominantly affects females of reproductive age. The prevalence of SLE among Asians is estimated to be 47.8 per 100 000 population [1]. Improved medical care over the years has resulted in more women with SLE surviving into adulthood. Clinicians need to be competent in managing these women during pregnancy because women with SLE have normal fertility rates, unlike those suffering from most other chronic medical illnesses. SLE causes significant morbidity to the mother and fetus throughout pregnancy: recurrent miscarriage, life threatening thrombo-embolic phenomena, preeclampsia, foetal growth restriction (FGR) and neonatal lupus. SLE, which is a T helper cell 2 driven illness, also tends to flare up during pregnancy due to a shift from a predominantly T helper 1 to a T helper 2 cellular response [1].

Since 2005, in the district of Gampaha alone, SLE has accounted for one maternal death every year for five consecutive years (personal communication, MO/MCH, office of the Regional Director of Health Services, Gampaha, Sri Lanka). This is probably an underestimation of the burden, as maternal mortality due to conditions such as cerebral thrombosis or fulminant liver failure which are manifestations of SLE may not be attributed to the disease. Given the dearth of obstetric physicians in Sri Lanka, all clinicians should be competent to advise on adequate disease remission to women with SLE contemplating pregnancy and to suspect and manage SLE during pregnancy. This includes preconceptional counselling (including advice against pregnancy), advice on contraception and adequate monitoring of disease activity during pregnancy.

### Preconceptional counselling

Preconceptional counselling is mandatory for all women with SLE contemplating pregnancy and is important in determining a successful pregnancy outcome. First, suitability for pregnancy should be assessed. Childbearing should not be contemplated in women with pulmonary hypertension [3] and those with lupus nephritis with a baseline serum creatinine  $>250\mu\text{mol/l}$  [4]. Pregnancy in the presence of renal impairment with baseline creatinine  $<250\mu\text{mol/l}$  should not be discouraged, though the couple should be informed of the risk of an adverse pregnancy outcome as foetal loss, preeclampsia and FGR are known to occur when baseline serum creatinine is  $125\text{--}250\mu\text{mol/l}$  [4].

Once the woman is deemed suitable for pregnancy, activity of the disease should be assessed, as there is evidence that women who become pregnant

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with active disease experience flares more often with higher morbidity and mortality compared to those who conceive while in remission [5]. A thorough clinical evaluation coupled with laboratory parameters (complement 3 and 4 levels, dsDNA titres) will help determine the activity of the disease. Those with active disease on prednisolone >0.5 mg/kg/d should delay pregnancy [6]. Various scores have been formulated in order to standardise the assessment of SLE activity during pregnancy. The Lupus Activity Index in Pregnancy (LAI-P) assesses disease activity in pregnancy and is one of the few scores that have been validated [7]. The score is also very useful for early detection of disease flares during pregnancy.

Once disease activity is assessed, women with active disease need modification of their drug regime and those in disease remission should be advised to conceive only after six months following the last flare. A suitable contraceptive method should be used until such time. The oral contraceptive pill (OCP) which was earlier forbidden for women with SLE, has been found to be safe in a recent randomised controlled trial which showed that use of the OCP does not significantly increase the disease activity, or risk of disease flares, in women at low risk for thrombosis having stable or inactive disease [8]. This study is likely to revolutionise contraception in SLE as the OCP has a higher acceptance rate among our women compared to barrier methods, which in the past were the most favoured.

In the presence of anti-Ro and anti-La antibodies, women with SLE need to be counselled about the risk of neonatal lupus [9]. Review of drugs (immunosuppressives, antimalarials, antihypertensives and anticoagulants) prior to conception is mandatory to avoid teratogenicity. Nonsteroidal anti-inflammatory drugs (NSAIDs) which are commonly given for symptom relief should be withheld during the last trimester due to risk of premature closure of the ductus arteriosus [10]. Prophylactic steroids in a woman in disease remission has no place, as this does not reduce SLE flares during pregnancy [11].

#### **Antenatal care**

Certain symptoms and signs which may suggest a SLE flare could be due to the physiological state in normal pregnancy [7]. Facial erythema, arthralgia, proteinuria and thrombocytopenia are normal physiological findings in pregnancy, and need cautious interpretation in a pregnant woman with SLE. Elevated ESR (upto 40 mm) and serum complement components C3, C4 and CH50 (which rise by 10-50%) are also normal findings in pregnancy [7]. Therefore, active components of serum complement should ideally be measured to gauge disease activity during pregnancy. Lymphopenia, but not leucopenia, should be considered an indicator of SLE activity in pregnancy, because a neutrophil leucocytosis can occur in the third trimester.

Women detected to have either anti-Ro or anti-La antibodies should be offered serial foetal echocardiograms between 16-24 weeks of gestation [12]. When incomplete heart block is detected in utero, 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 [13].

The presence of lupus nephritis and/or antiphospholipid syndrome adversely influences pregnancy outcome in SLE. In their absence disease flares occur in 30-60% of pregnant patients, but are usually mild or moderate and predominantly affect the skin and joints [11]. These can be managed with NSAIDs, low dose prednisolone (10 mg/day) and hydroxychloroquine. Lupus patients have an increased risk of preeclampsia (5-38%) compared to women without SLE [14]. This risk is further aggravated in the presence of pre-existing hypertension, nephritis and antiphospholipid antibodies. Superimposed

preeclampsia should be differentiated from a flare of lupus nephritis associated with hypertension, as misdiagnosis will endanger life. An active urinary sediment, reduced levels of serum C3, C4 and C50 and elevated levels of dsDNA favour a diagnosis of lupus nephritis [7]. Low to moderate dose aspirin and low dose heparin should be given as prophylaxis against preeclampsia and thrombosis to women with antiphospholipid syndrome and patients at risk for preeclampsia (i.e. those with lupus nephritis with or without hypertension). The combination of these two drugs has been shown to reduce adverse maternal and foetal outcome [15].

The fetal outcome in lupus pregnancies is complicated by a high rate of abortions (6-35%), still births, prematurity and FGR [16]. The predictive factors for fetal wastage include active lupus nephritis, previous history of foetal death, and the presence of antiphospholipid antibodies. Maternal hypertension and high dose steroids are predictors of prematurity and FGR [12].

### Intrapartum and postpartum care

When the mother has been on a dose of steroids equivalent to >7.5 mg of prednisolone daily for more than two weeks, parenteral steroids will be required to cover the stress of labour and delivery regardless of the mode of delivery [4]. Close monitoring of activity should be continued into the puerperium as disease flares are known to occur even in women who had no active disease in the antenatal period. Nursing mothers can continue to take prednisolone and hydroxychloroquine if required, while methotrexate, azathioprine, cyclophosphamide and cyclosporine A should be avoided [12].

With the existing facilities in our state hospitals most pregnant women with SLE could be managed adequately, and an expert opinion sought only in complicated cases or when facilities are inadequate to manage a flare. Though associated with potential risks and complications, pregnancy outcome in women with SLE is much better when planned during disease remission and under close supervision by a competent and dedicated team.

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