INVITED ARTICLE

PREGNANCY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

O A C Viegas, M L Boey

ABSTRACT

The view that SLE in pregnancy is associated with poor maternal and perinatal outcome is generally accepted. Consequently, there is a mistaken but commonly held belief that termination of such pregnancies will safeguard maternal health. However, because of advances in diagnostic technology, improved antenatal and neonatal surveillance, wider treatment options and a clearer understanding of the pathological processes involved, such a view is no longer tenable.

This article outlines the changes in obstetric practice that have made pregnancy in women with SLE a relatively safe process. In particular, it emphasizes the need for a multidisciplinary approach to caring for such pregnancies. It also draws out some of the experiences we have had with the management of such pregnancies in Singapore that will reinforce the view that women with SLE can reproduce safely and successfully given appropriate care.

Keywords: Systemic Lupus Erythematosus, antiphospholipids, intrauterine growth, congenital complete heart block.

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INTRODUCTION

In current obstetric practice, there is an unfortunate myth that pregnancy is contraindicated in systemic lupus erythematosus (SLE). Patients are given the impression that they have a rapidly progressive and probably fatal disease. Earlier studies of pregnant SLE patients with a high incidence of intra or postpartum flares of the disease have resulted in further misconceptions regarding the advisability of pregnancy. Much of this bleak outlook has been generated by the early work of Merrel and Schulman that reported a median survival of less than four years for SLE sufferers[1]. Since their report, several advances have been made with regard to the management of patients with SLE and these have transformed the long term outlook for women with SLE. These advances include the advent of corticosteroid and immunosuppressive therapy, availability of serological analyses for early diagnosis and surveillance and improvements in antenatal and neonatal care. Indeed, women with SLE are no less fertile than the general population and pregnancy is usually uncomplicated with virtually no increased risk of SLE flares during pregnancy and only a small risk of SLE manifesting in the baby. However, there are a minority of patients that are at higher risk of increased fetal loss. They include those with active disease, renal involvement, and women with circulating phospholipid antibodies (ie the lupus anticoagulant or the anticardiolipin antibody). In these circumstances, a multidisciplinary approach to management involving obstetricians, neonatologists, rheumatologists and nephrologists will help enhance successful outcome for mother and infant.

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EFFECT OF PREGNANCY ON SLE

The effect of pregnancy on SLE is controversial. A common belief is that one-third of patients improve, a third stay the same, and the remaining third worsen. However, Nossent and Swaak[2] observed that pregnancy during SLE was accompanied by disease exacerbations in up to 74% of the patients. Lockshin[3] showed that worsening of SLE is uncommon in pregnancy with less than 13% of patients experiencing disease exacerbation. In a series by Mintz and Rodriguez-Alvarez[4], 60% of cases were associated with disease flare, which was not significantly different from flares in non-pregnant patients.

Pregnancy conceived during active SLE or lupus renal disease is likely to run a more severe course. Exacerbations occur in about 50% of patients. Pregnancy does not appear to influence the long term prognosis of SLE. In general, SLE patients who become pregnant have a more favourable prognosis than those who do not. Furthermore, successive pregnancies do not necessarily affect an individual in the same way.

Pregnancies complicated by SLE are associated with a higher rate of fetal wastage, prematurity, dysmaturity and neonatal complications.

Fetal Wastage

Pregnant women with SLE are known to have an increased rate of fetal wastage[5-7]. Many reasons for the increased abortion rate have been postulated. These include maternal genetic traits leading to fetal abnormalities and abortion, viral particles in the placenta, immunological incompatibility between mother and fetus, transplacental influx of maternal autoantibodies and systemic vasculitis. The current view is that the risk of wastage is highest in women who have circulating lupus anticoagulant (LA)[8-10]. In these women, such complications are associated with arterial or venous thrombosis. Thrombosis may occur, in particular in the placental vasculature, [8,10,11]. LA may also interfere with the production of prostacyclin by vessel walls and tissues including pregnant myometrium [8,12] thereby having an adverse effect on pregnancy outcomes.

In our own series the spontaneous abortion rate of 19% was higher than observed in other series (cumulative mean)[13]

This could reflect our unwillingness to recommend termination of pregnancy in the absence of strong contraindications. We have experienced no intrauterine fetal death. This was attributed to improved antenatal surveillance and ultrasound assessment of fetal growth and blood flow patterns. Improved neonatal support has also given us the confidence to intervene preterm. Five births occurred before 37 weeks of which 3 were by elective caesarean section. Where biochemical markers of disease activity and antenatal evaluation have been normal, we have been able to prolong pregnancy to term giving a term delivery rate of 57% and an overall live birth rate of 81%.

Intrauterine Growth (Table I, Fig 1)

There was a significantly lower mean crude birthweight among babies born to mothers with SLE. Some of this deficit in growth could be attributed to a significantly shorter mean gestational age in these infants but the smaller placentae in SLE pregnancies suggest that intrauterine growth failure is also important. Other investigators have attributed this intrauterine growth retardation to placental insufficiency induced by vasculitis or derangement in estrogen metabolism[14].

Fig 1 - Crude Birthweight in SLE Pregnancy (Mean +- SE)

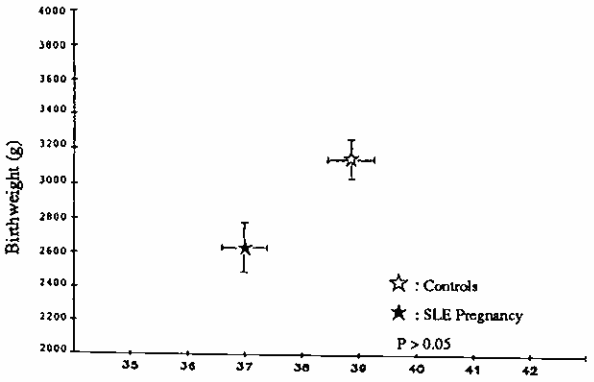

Table I - Intrauterine Growth

Parameter studies Mean (SD)	SLE Pregnancy n = 17	Matched Control* n = 17	P value
Gestational age (wks)	36.9 ± 1.4	38.4 ± 1.5	< 0.01
Crude birthweight (g)	2639 ± 545	3134 ± 364	< 0.01
Placental weight (g)	440 ± 101	560 ± 147	< 0.01
% Low birth weight	35.3	5.8	< 0.01

* Control matched for age, ethnic group parity and fetal sex

In addition to fetal wastage as already described there exists the problem of sudden fetal death at around 36 weeks of gestation. This appears to be associated especially with pre-eclampsia and renal disease. Circulating anti-cardiolipin (aCL) Ab is thought to be responsible. This manifests antenatally as severe fetal bradycardia, which results finally in fetal death.

The risk of sudden fetal demise at 36 weeks gestation, along with the other attendant problems of an SLE pregnancy, worsening pre-eclampsia and renal disease prompt early delivery. Steroid-induced diabetes is also a consideration.

Neonatal Lupus Syndrome

This is a rare syndrome originally described by McCuiston and Schoch in 1954[15]. The syndrome is related to the passage of maternal antibodies across the placenta to the fetus, and its resolution usually occur within six months when the infant becomes seronegative. The majority of patients with the Neonatal Lupus Syndrome are born to mothers with SLE who have Ab to Ro (SSA), La (SSB) or nRNP. However, the risk of an affected child in mothers with SLE and/or these autoantibodies has not been defined.

If a baby is born with any of the features of the Neonatal Lupus Syndrome, the mother should be carefully investigated for SLE. These children may go on to develop SLE in later life, but this is rare. Various manifestations of SLE in the neonates have been reported:

i) Discoid Lupus Erythematosus: These lesions may be present at birth or appear at the age of about one month. They are usually transient and disappear within 6 months leaving no scars.

ii) Thrombocytopenia: The pathogenesis of thrombocytopenia is unknown and has been little studied. aCL may be involved.

iii) Cardiac Abnormalities: Both structural abnormalities and congenital heart block are seen. Structural defects occur early in the development of the heart, whereas the isolated congenital heart block associated with Ro(SSA) and La(SSB) autoAb occurs in the fetus during the late 2nd and 3rd trimester after the heart is fully developed. This is a permanent defect and many of these babies require pacemakers. The presence of these is linked to submyocardial deposition of Ig which may induce permanent fibrotic changes in the conduction system of the fetal heart. Myocarditis, fibroelastosis and pericardial effusions have all been described[16].

MANAGEMENT OF SLE AND PREGNANCY

Pre-Pregnancy Advice

This should represent the combined advice of both a physician and an obstetrician who have special interest in this field. The nature of the advice must depend on the severity of the disease and the importance of having a baby to the couple.

Ideally, patient-education should occur at initial diagnosis. Pregnancy, if desired, should be planned during periods of remission. When educated about the maternal and fetal implications of the disease, the patient is better prepared both for the intensive observation needed and possible obstetric or neonatal complications that might occur.

The prognosis is best if the patient is without renal, neurological or cardiac involvement, and has been in remission for at least six months. Thus, pregnancy is a relative contraindication in patients with active SLE, particularly those with cardiac involvement. These patients have a greater risk of worsening, increased fetal wastage and a limited life expectancy.

ANTENATAL MANAGEMENT

The following factors need to be established:

i) Accurate dating

There is a definite risk of prematurity and IUGR in these patients so gestational age needs to be established (ultrasound) as early as possible.

ii) Baseline assessment of severity

Clinical parameters, haematological indices (FBC, PT/APTT, KCT) and tests of renal function (urinalysis, serum creatinine, urine total protein and creatinine clearance) are the most useful. A rise in anti-dsDNA Ab frequently correlates with disease activity and depression of serum complement (C3 and

C4) is indicative of consumption of immune complexes and tends to correlate with tissue activity. The change in complement levels should be monitored. Serial levels of LAC and aCL may also be measured.

iii) Follow-Up Monitoring

Serial measurements of clinical parameters and laboratory investigations are necessary to detect any exacerbation, development of pre-eclampsia, or deterioration in function. Fetal growth should be monitored clinically and by serial ultrasound. Fetal well-being should be assessed by fetal movement charts, cardiotocography, and aCL levels. High levels of aCL are a sensitive and specific predictor of fetal distress[17] Non-periodic decelerations on the CTG may be an indicator of intrauterine compromise with bradycardia strongly suggesting impending fetal demise. Bradycardia may also indicate congenital heart block. The decelerations tend to occur long before oligohydramnios is found[18].

iv) Drug Treatment

There are no major differences in the way active disease should be treated in pregnancy. A tendency for the disease to relapse postpartum has been noted, so treatment must be continued and/or increased during this time. Early forms of treatment included preterm delivery of the infant. The use of combinations of immunosuppressive and anticoagulants is an alternative pharmacological approach that allows pregnancy to proceed further towards term.

Patients with active disease should receive immunosuppressants. Glucocorticoids are the mainstay of treatment, the smallest effective dose being used. Azathioprine or cyclophosphamide are added only when increasing doses of prednisolone are unable to suppress disease activity. Increased immunosuppression in women without a history of fetal death is probably unjustified.

Women with recurrent fetal loss represent a special group of patients. Lubbe et al (1983) have treated such LAC-positive patients with low dose aspirin and prednisolone[19]. In patients who failed to respond, the dose of steroid was increased and cyclophosphamide or azathioprine added. LAC and PT/APTT levels were monitored during therapy. The Ig levels were found to normalize within nine to 16 weeks of treatment. A combination of prednisolone, aspirin, dipyrimadole and heparin has also been used in order to prevent coagulation in decidual blood vessels[20]. High dose corticosteroid therapy is associated with adverse side effects. Women tend to become Cushingoid, hypertensive and diabetic. High titres of antibodies, absence of active disease and a previous negative history of fetal loss or thrombosis do not warrant immunosuppressive therapy.

DELIVERY

The timing of delivery depends on both the maternal and fetal status. Renal disease in the mother, especially associated with hypertension, will necessitate early delivery, the precise timing being dictated by the level of neonatal support available.

SLE per se is not indication for LSCS. Careful fetal monitoring should be employed during labour to minimize operative intervention. In our series, we have reported a 35.3% caesarean section rate. In patients with fetuses exhibiting CCHB induced by antiphospholipid antibodies, conventional electronic monitoring for fetal heart rate abnormalities becomes inappropriate so that in such cases, delivery is best conducted electively by caesarean section. This mode of treatment has the advantage of maximizing optimum facilities for the immediate medical or surgical treatment of the neonatal CCHB. Patients who have been on steroids will require intravenous hydrocortisone.

Postpartum Management

The puerperium is a high risk period for exacerbation of SLE. Steroid therapy should be maintained for at least six to eight weeks before careful gradual reduction. Breast-feeding is discouraged if the patient is on immunosuppressive or anti-coagulant.

Contraception

While present day multi-disciplinary care of SLE patients in pregnancy has improved the prognosis for both mother and child, the course of SLE is chronic, unpredictable and sometimes grave, and many patients decide to avoid pregnancy.

The IUCD is not recommended because of the risk of infections in immunosuppressed patients. Oestrogen-containing pills have been associated with thrombosis, hypertension and possible exacerbation.

Thus, the use of barrier methods seems prudent. Progesterone-only pills are also acceptable and the recent advent of progesterone implants offers a more convenient method of contraception. Routine follow-up should include regular PAP smears as immunosuppression is known to predispose to dysplastic changes in cervical epithelium.

Termination of Pregnancy

There is currently no clear evidence that termination of pregnancy improves maternal outcome even in cases with lupus nephritis[21].

Termination of pregnancy should not be performed in the hope of reversing the disease process[22,23]. Decisions to recommend continuation or termination of pregnancy have to depend on careful individual assessment of the disease activity and the importance of the pregnancy to the patient and her husband.

CONCLUSION

Many of the pathophysiological processes involved in SLE are still largely unknown. To effect an improvement in the outcome of pregnancy, obstetricians will need to be guided by physicians and rheumatologists.

The development of "shared care" between obstetrician and physician is therefore essential. Similarly the utilization of advanced technology for antenatal fetal surveillance and the improvement of neonatal support services are also of integral importance for the care of pregnancies complicated by SLE. The elucidation of the precise roles of anti-phospholid antibodies and the anti-Ro antibody will influence treatment strategies resulting in improved outcomes for mother and fetus. Whilst the mainstay of treatment includes steroid therapy, aspirin and in selected cases immunosuppressive agents (azathioprine), other treatment modalities have been reported. These include the intravenous infusion of gamma-globulins in the treatment of recurrent fetal loss associated with circulating lupis anticoagulant[24] and the use of plasma exchange to remove the anticardiolipin antibody therapy prolonging gestational age in patients with anticardiolipin syndrome[25].These modes of therapy are at best experimental.

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