

Outcome of Pregnancy in Asian Women with Systemic Lupus Erythematosus: Experience of a Single Perinatal Centre in Singapore

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Abstract

Objective: To study maternal and fetal outcomes in women with systemic lupus erythematosus (SLE). **Materials and Methods:** Retrospective study of 27 pregnancies in 18 women with SLE in a single centre. **Results:** The mean age was 30 years and most patients were nulliparous. Twenty-six of 27 pregnancies were in disease remission at the time of booking. Renal impairment was present in 7 pregnancies (6 women), of whom 2 were in end-stage renal disease on dialysis. Gestational diabetes developed in 4 pregnancies. There were 6 cases of pre-existing hypertension and 5 with superimposed pre-eclampsia. One woman developed intrapartum eclampsia. Two women had secondary antiphospholipid syndrome (APS) and suffered late fetal losses; in addition, they also developed SLE flares in the form of autoimmune haemolytic anaemia in the postpartum period. There was no maternal mortality. There was one termination of pregnancy for severe renal disease. The median gestational age at delivery was 38 weeks (range, 24 to 40 weeks) and the mean birth weight was 3047 g; the median Apgar scores were 8 and 9 at 1 and 5 minutes of life, respectively. There were 5 cases of intrauterine growth restriction (IUGR), 4 of which occurred in women with renal impairment. There were no cases of congenital heart block or neonatal lupus. There was a late fetal loss at 24 weeks in a woman with secondary APS. There were 2 preterm deliveries (7.4%) due to intervention for IUGR. **Conclusion:** Good pregnancy outcomes can be expected in women with SLE in remission. Pre-pregnancy counselling is crucial to achieve this. All pregnancies should still be considered high risk and be managed jointly between the obstetricians, the perinatologists and the physicians. In particular, those with renal impairment are at increased risk of IUGR, superimposed pre-eclampsia and preterm births. Co-existing APS augurs a poorer prognosis for pregnancy outcome, and may present atypically as autoimmune haemolytic anaemia in the postpartum period.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic connective tissue disease with a reported prevalence of 5 to 100/100,000.¹⁻⁴ Women are affected much more commonly than men (ratio 9:1), particularly those in the child-bearing age (15:1).¹ The incidence in women of child-bearing age is 1 per 1000 women and may be increasing.¹ SLE in pregnancy poses serious clinical challenges to the obstetrician as it is associated with both maternal and fetal morbidity and mortality.⁵

Objective

The objective of this study was to audit the experience of the High Risk Pregnancy Clinic at the Department of

Obstetrics and Gynaecology, Singapore General Hospital (SGH) in its management of pregnant women with SLE in terms of pregnancy outcome.

Patients and Methods

At the SGH, all women with SLE in pregnancy are managed in the High Risk Clinic.

Antenatal care of these women are jointly managed by the high-risk obstetricians and physicians. The diagnosis of SLE is made based on the 1982 American College of Rheumatology (ACR) criteria classification.⁶ Antenatal care is based on protocol-directed guidelines to ensure that potential maternal and fetal complications are detected. At booking, the viability and dating of the pregnancy is

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TABLE I: DRUGS USED IN SLE PREGNANCIES

Patient	Clinical condition	Drugs used
A	ESRF Haemodialysis	s/c heparin 5000 units bd and throughout pregnancy Methyldopa 500 mg tds throughout pregnancy
B	SLE with hypertension	s/c heparin 5000 units bd started at booking (1 st trimester) and throughout pregnancy Methyldopa 250 mg tds throughout pregnancy
C	ESRF CAPD	s/c heparin 5000 units bd throughout pregnancy Methyldopa 500 mg tds throughout pregnancy
D	Hypertension Nephrotic syndrome	Methyldopa 375 mg tds, increased to 500 mg tds at 28 weeks Prednisolone increased to 10 mg od from booking (1 st trimester)
E	Thrombocytopaenia	Prednisolone 5 mg od throughout pregnancy
F	Thrombocytopaenia	Prednisolone 5 mg od throughout pregnancy
G	Lupus nephritis: Class 4 segmental sclerosing nephritis	Prednisolone 5 mg od prior to pregnancy, increased to 10 mg od on booking
H	Antiphospholipid syndrome: Positive lupus anticoagulant and high titres for anti- cardiolipin antibodies, 2 previous mid-trimester fetal losses	Aspirin 100 mg od and s/c heparin 5000 units od started at 18 weeks
I	Antiphospholipid syndrome: Positive lupus anticoagulant	1 st pregnancy: stillbirth at 31 weeks 2 nd pregnancy: aspirin 100 mg od started from 13 weeks' gestation, declined heparin, lost to follow-up
J	Positive anti-Ro antibody	On maintenance prednisolone 5 mg od. Hydroxychloroquine stopped and aspirin 100 mg od started on diagnosis of pregnancy (1 st trimester)
K	SLE in remission	Maintenance prednisolone 4 mg od Aspirin 100 mg od started in pregnancy (1 st trimester)

CAPD: continuous ambulatory peritoneal dialysis; ESRF: end-stage renal failure; s/c: subcutaneous; SLE: systemic lupus erythematosus

confirmed by ultrasound. A thorough history and physical examination is taken to determine disease activity or remission status together with a review of the drugs the patient is taking. All patients undergo baseline and serial investigations including full blood count, renal and liver panel tests, C-reactive protein, anti-nuclear antibody and double-stranded DNA titre, extractable nuclear antigens (anti-Ro and anti-La antibodies). Those with positive anti-Ro antibodies are referred for serial detailed fetal echocardiography to detect any evidence of congenital heart block. Overlapping connective diseases, in particular the antiphospholipid syndrome (APS), are screened for with the lupus anticoagulant and anticardiolipin antibodies IgG and IgM assays.

Renal involvement is already determined in this group of women prior to their becoming pregnant. On review, the diagnosis of renal disease in this group of women was based on clinical criteria, i.e. proteinuria and elevated serum urea and creatinine levels, unless the woman had a renal biopsy which allowed a specific histological classification. Women with renal disease are co-managed with the hospital renal physicians with regular assessment of renal function. Arrangements are made for those with end-stage renal failure to have more frequent dialysis.

Antenatal checkups are conducted every 2 weeks and weekly from the 36 weeks of gestation, with a view to early detection of SLE flares and pre-eclampsia. Gestational diabetes is screened for at 28 weeks of gestation if the woman is on corticosteroids and if she meets standard obstetric criteria. Regular fetal growth ultrasound scans with umbilical artery Doppler assessment are done to detect evidence of fetal growth restriction. Decisions regarding timing and mode of delivery are based on medical and obstetric considerations. All deliveries are conducted in the high-risk labour ward with the obstetric anaesthetist and neonatologist in attendance. In the postpartum period, women are nursed in the high-dependency postnatal ward.

This retrospective review includes pregnant women with SLE who were seen at the high-risk clinic of SGH between 1994 and 1999. The high-risk clinic database were searched to identify these patients' casenotes which were retrieved and reviewed. The following outcome measures were recorded: demographic data (age, parity, disease status at booking, SLE flares during pregnancy and the puerperium, drugs used), medical complications (renal disease, haematological disease, gestational diabetes, superimposed pre-eclampsia), fetal complications [congenital anomalies, miscarriages, stillbirths, intrauterine growth restriction

(IUGR)] and delivery data (gestational age at delivery, mode of delivery, birth weight, maternal mortality). The criteria for the identification of SLE flares were based on the detection of new onset anaemia, lymphopaenia, a rise in double-stranded DNA titres or new onset positivity of antinuclear antibody, through serial monitoring during pregnancy and in the puerperium, in association with

TABLE II: MEDICAL COMPLICATIONS (PRE-EXISTING OR SUPERIMPOSED) IN 27 PREGNANCIES

Medical complication	n (%)	Comments
Renal (diagnosed on clinical criteria)	7 (25.9)	5 are hypertensive
Lupus nephritis	5	1 woman with nephrotic syndrome (2 pregnancies) 1 with Class 4 segmental sclerosis
ESRF requiring haemodialysis	1	LSCS at 31 weeks for IUGR
ESRF requiring CAPD	1	Normal vaginal delivery at term
Haematological	9 (33.3)	
Anaemia (excluding thalassaemia & iron deficiency)	7	
Autoimmune haemolytic anaemia	2	Both women developed AIHA acutely in the puerperium requiring blood transfusions. Both women were in disease remission at conception and throughout their pregnancies.
Immunological	3 (11.1)	
Antiphospholipid syndrome	2	Both women with bad obstetric history; one woman's pregnancy resulted in an intrauterine death at 24 weeks; the other lost to follow-up
Anti-Ro positive block	1	Fetus did not have congenital heart block
Cardiac	1 (3.7)	
Cardiomyopathy	1	Echocardiography demonstrated good systolic function
Gestational diabetes mellitus	4 (14.8)	1 required insulin treatment
Hypertensive disorders of pregnancy	12 (44.4)	
Pre-existing hypertension	6	5 have renal disease
Superimposed pre-eclampsia	5	3 have renal disease
Eclampsia	1	Antepartum did not have hypertension. Developed eclampsia at 2 nd stage of labour; emergency LSCS done and a healthy baby delivered; woman made an uneventful recovery.

AIHA: autoimmune haemolytic anaemia; ESRF: end-stage renal failure; IUGR: intrauterine growth restriction; LSCS: lower segment caesarean section

evidence of renal deterioration e.g. increasing proteinuria and decreasing creatinine clearance.

Results

A total of 18 women with SLE were identified. One woman was later lost to follow-up. There were 27 pregnancies in these 18 women.

The mean age of the patients was 30 years (± 3.7 years) and the median parity was 0 (range, 0 to 2). Twenty-six of the 27 pregnancies were in disease remission. Table I provides details of 10 pregnancies in which drugs were administered.

The types and frequency of medical complications encountered during the 27 pregnancies are shown in Table II. Table III provides details of 6 patients (7 pregnancies) with renal disease, 2 of whom had end-stage renal failure—1 was on haemodialysis while the other received peritoneal dialysis. Seven pregnancies had anaemia (haemoglobin <11 g/dL); thalassaemia and other haemoglobinopathies were excluded. None required blood transfusions. APS was diagnosed in 2 women based on the Sapporo diagnostic criteria.⁷ Both women had bad obstetric histories—one had suffered 2 previous intrauterine deaths at 24 and 28 weeks, and the other had a previous stillbirth at 31 weeks. The latter was lost to follow-up. Another woman was found to

TABLE III: CLINICAL DETAILS OF WOMEN WITH RENAL INVOLVEMENT (n = 6)

Patient	Type of renal involvement	Renal function (at booking)	Pregnancy outcome
A	ESRF on haemodialysis	Cr 123 μ mol/L Uric acid 478 μ mol/L	Elective CS at 28 weeks for IUGR BW 1495 g; LB
B	Lupus nephritis	Cr 700 μ mol/L Uric acid 549 μ mol/L	TOP
C	ESRF on CAPD	Cr 220 μ mol/L	SVD at 35 weeks BW 2060 g; LB
D	Nephrotic syndrome	Cr 70-90 μ mol/L for both pregnancies UTP 6 g/day	1st pregnancy: SVD 38 weeks, BW 2010 g; LB 2nd pregnancy: SVD 37 weeks, BW 2355 g; LB
E	Lupus nephritis	Cr 85 μ mol/L CCT 108 mL/min	SVD 37 weeks BW 3880 g; LB
F	Class 4 segmental sclerosis	Cr 75 μ mol/L CCT 60 mL/min UTP <0.1 g/day	SVD 37 weeks BW 2170 g; LB

BW: birth weight; CAPD: continuous ambulatory peritoneal dialysis; CCT: creatinine clearance test; Cr: serum creatinine; CS: caesarean section; ESRF: end-stage renal failure; IUGR: intrauterine growth restriction; LB: livebirth; Lupus nephritis: unclassified renal involvement in SLE; SVD: spontaneous vaginal delivery; TOP: termination of pregnancy; UTP: 24-hour total urinary protein

TABLE IV: FETAL OUTCOMES (n = 27)

Fetal outcome	No. (%)	Comments
No. of term pregnancies	22 (81.5)	
No. of preterm pregnancies	2 (7.4)	
Termination of pregnancy	1 (3.7)	Severe renal disease
Intrauterine death	2 (7.4)	Both mothers had antiphospholipid syndrome
Congenital abnormalities	0	
Intrauterine growth restriction	5 (18.5)	Birth weight range, 1495 to 2405 g 4 babies were born to women with renal disease (1 on haemodialysis, 1 on CAPD, 1 with nephrotic syndrome, 1 with class 4 segmental sclerosis)
Median gestational age (weeks)	38	Range 24 to 40 weeks
Median Apgar score at 1 minute of life	8	
Median Apgar score at 5 minutes of life	9	
Mean birth weight (g)	3047 ± 557	

CAPD: continuous ambulatory peritoneal dialysis

have anti-Ro antibodies but was serologically negative for Sjogren's syndrome. There were 4 cases of gestational diabetes diagnosed in this case series, of which only 1 required additional insulin treatment. Pre-existing hypertension was present in 6 women in our series, of whom 5 had underlying renal impairment. Five women developed superimposed pre-eclampsia, of which 3 had pre-existing renal impairment. One woman developed intrapartum eclampsia.

Tables IV and V summarise fetal and delivery outcomes respectively. There was 1 social termination of pregnancy and 1 stillbirth at 24 weeks. No cases of therapeutic abortion were performed. There were 22 term and only 2 preterm deliveries. The latter were due to intervention for IUGR. The overall mean birth weight was 3047 g and the median Apgar scores were 8 and 9 at 1 and 5 minutes of life, respectively. The caesarean section rate was 19.2%. These were performed largely for obstetric indications.

Discussion

The majority of women with SLE that were seen by us were young and in their first pregnancies. Diagnosis of SLE was made before pregnancy in all cases. This, coupled with the observation that all were in disease remission at the time of booking, demonstrates the importance and benefit of effective pre-pregnancy counselling to ensure optimum pregnancy outcome.

TABLE V: DELIVERY OUTCOMES (n = 25)*

Delivery outcome	No. (%)	Comments
Normal vaginal delivery	18 (72.0)	
Instrumental delivery	2 (8.0)	
Caesarean section	5 (20.0)	Indications: 1 for IUGR, 2 for CPD, 1 for breech presentation and 1 for eclampsia
Maternal mortality disproportion;	0	

* From the cohort of 27 pregnancies: 1 TOP, 1 lost to follow-up
CPD: cephalopelvic disproportion; IUGR: intrauterine growth restriction;
LSCS: lower segment caesarean section; TOP: termination of pregnancy

Six of the women required maintenance prednisolone to remain in disease remission. There were no congenital fetal anomalies seen in this small series, which is not unexpected given that the dose taken was small (<10 mg/day) and that oral prednisolone is largely metabolised in the placenta so that little actually crosses the placenta to the fetus.⁸ One of our patients stopped hydroxychloroquine upon diagnosis of her pregnancy, given the lack of data on fetal safety at the time. Nevertheless, it would be interesting to see if hydroxychloroquine will paradoxically assume an increasing role in maintaining disease remission in pregnancy in the future, given a recent randomised trial in pregnancy demonstrating its steroid-sparing effect and superior disease control and fetal safety.⁹

Renal involvement by SLE complicated 7 pregnancies in 6 women and was the second most common complication after non-specific anaemia. All of these were pre-existent before pregnancy; however, only 1 was histologically characterised as class 4 segmental sclerosis, the rest were diagnosed purely on clinical criteria as no renal biopsies were performed. As shown in Table III, the serum creatinine level at the outset of pregnancy has a critical influence on the pregnancy outcome. One woman with serum creatinine level of 700 µmol/L was counselled regarding the poor prognosis of her pregnancy and she elected for termination of the pregnancy. Most of the other women had mildly impaired renal function with serum creatinine levels ranging from 75 to 123 µmol/L at booking (Table III). This group did best and carried their pregnancies to term with appropriately grown fetuses. This compares favourably with a recent French study looking at fetal and maternal outcomes in SLE mothers with renal disease.¹⁰ The two women in our series with end-stage renal disease did remarkably well in carrying their pregnancies to at least 31 weeks' gestation. This is due to the improved serum creatinine levels achieved by the increased frequency of dialysis in anticipation of the increased demands placed by the physiological changes of pregnancy. One of the women,

who was on peritoneal dialysis, managed to continue her pregnancy till 36 weeks, giving birth vaginally to a good sized baby. This was only possible through close collaboration with the renal physicians, and this highlights the importance of managing these high-risk pregnancies in centres with access to multidisciplinary expertise.

Four of the 5 pregnancies complicated by IUGR had renal disease, showing that the presence of renal impairment is a strong predictor for IUGR. This observation is consistent with most case series of SLE pregnancies in the literature,^{11,12} and emphasises the need for all women with renal involvement to have close serial growth scans and tests of fetal well-being.

There were only 2 cases of preterm births giving a low incidence of prematurity (7.4%) compared to that reported in the literature for an Asian population.¹³ This is due to the majority of the women in our series being in disease remission, thus allowing the pregnancies to continue to term. In these 2 cases, the mothers also had renal impairment with growth restricted fetuses; hence, the prematurity was iatrogenic as the delivery was expedited for fetal reasons.

The fetus of the mother with positive anti-Ro antibodies did not develop complete congenital heart block. This is not surprising as the risk of congenital heart block is only about 2%, according to a recent prospective study.¹⁴ In this series, there were no cases of neonatal lupus observed in the babies delivered; again, this may be due to the women being in disease remission.

APS is a recognised cause of pregnancy complications, including miscarriage, fetal death and pre-eclampsia.¹⁵ Secondary APS occurs in 20% to 35% of SLE cases and appears to augur a particularly bad prognosis in terms of perinatal outcome.¹⁶ One of the 2 patients with this condition in our series tested positive for lupus anticoagulant and high titres of anticardiolipin antibodies also had 1 stillbirth at 31 weeks in her first pregnancy, thereby satisfying the Sapporo criteria for diagnosing APS.⁷ She was prophylactically started on aspirin 100 mg od in her second pregnancy but was lost to follow-up. The second woman with APS had 2 previous stillbirths. Unfortunately, she suffered yet another intrauterine death at 24 weeks' gestation despite being on both low-dose aspirin and heparin treatment. However, this combination was only commenced at 13 weeks as she booked late. Interestingly, in the 2 controlled studies in the literature which suggest that heparin plus aspirin is better than aspirin alone, the majority of the patients suffered from recurrent early miscarriages rather than late fetal losses; moreover, SLE was excluded in these studies.^{17,18} There may well be different mechanisms operating in secondary APS from the primary syndrome. Placental studies demonstrate high rates of decidual vasculopathy and thrombosis and extensive placental

infarction in SLE pregnancies, with double positivity for lupus anticoagulant and antiphospholipid antibodies, suggesting that they form a particular strong risk factor for fetal death.¹⁹ For future pregnancies, our patient may benefit from earlier treatment—as soon as she is pregnant or by receiving treatment periconceptually. Giving a higher dose of heparin or novel therapies, such as double filtration plasmapheresis,²⁰ may also be alternative options.

Of even greater interest is the observation that both these patients with secondary APS developed acute autoimmune haemolytic anaemia in the postpartum period after delivering stillbirths, suggesting that perhaps SLE flares in this subgroup of SLE mothers may present atypically. Any unexplained fall in haemoglobin in the postpartum period in the absence of postpartum haemorrhage should therefore prompt relevant investigations, including a Coombs test, peripheral blood film and haptoglobin towards excluding this diagnosis. These cases illustrate the importance of screening for the APS in pregnancies complicated by SLE.

Distinguishing superimposed pre-eclampsia from an SLE renal flare is a well-known clinical challenge, as the features of hypertension, proteinuria, thrombocytopenia and hyperuricaemia are common to both. Indeed, pre-eclampsia may be missed in anuric end-stage renal disease as testing for proteinuria is not possible. Hypocomplementaemia, which would suggest a SLE flare, is probably the clinically useful distinguishing test. Using this criterion, we observed 5 cases of superimposed pre-eclampsia, of whom 3 had pre-existing renal disease. The importance in not missing pre-eclampsia in the setting of renal disease is that pre-eclampsia may follow an unpredictable progressive course with multi-system manifestations that are potentially life-threatening. One patient in our series developed intrapartum eclampsia. The management is different for the two conditions: pre-eclampsia is cured by delivery whereas SLE flares is controlled with immunosuppressive therapy.

In this difficult clinical dilemma, an argument can be made for delivery if the gestation has reached at least 28 weeks. This would allow the resolution of pre-eclampsia, and if the deterioration was due to a SLE flare, immunosuppressive agents such as cyclophosphamide, which would otherwise be contraindicated in pregnancy, can be used. Clearly, the problem in this undertaking would be fetal prematurity, and this highlights the need for such pregnancies to be managed in centres with neonatal special care facilities.

We did not see any renal flares and indeed none of our patients with renal impairment developed renal deterioration either during or after pregnancy in the postpartum period.

The caesarean section rate of 20% in our series is lower than that reported in the literature for a local population

(44%).²¹ The indications for caesarean section were essentially obstetric in nature, and this is in part due to the majority of women being in disease remission.

We did not observe any maternal mortality in this series. Again, this is a reflection of the disease remission and timely intervention of acute catastrophes such as eclampsia and the autoimmune haemolytic anaemia.

Conclusion

Women with SLE can be advised that they can have safe and successful pregnancies with the disease in remission at the time of conception. Pre-pregnancy counselling towards achieving this is vital. Nonetheless, all expectant women with SLE should be managed as high-risk pregnancies with optimal care provided by joint clinics involving both obstetricians and physicians in a tertiary centre with good neonatal support. In particular, women with renal involvement are at higher risk of IUGR and preterm deliveries and warrant more intensive fetal surveillance, with more frequent growth ultrasound scans and Doppler ultrasound assessment of the umbilical artery flow. The possibility of superimposed pre-eclampsia must be considered and serum complement assays may be useful adjuncts to try to distinguish it from renal flares. All pregnancies with SLE should be screened for the coexistence of the antiphospholipid antibodies as this may be associated with a worse perinatal prognosis, and vigilance is important to detect the development of SLE flares which may present atypically as autoimmune haemolytic anaemia.

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