Maternal and fetal complications of systemic lupus erythematosus

Matthew Cauldwell MBBS BSc,a,* Catherine Nelson-Piercy FRCP FRCOGb

aGuy’s and St Thomas’ NHS Foundation Trust, Maternity Services, St Thomas’ Hospital, 10th Floor, North Wing, Westminster Bridge Rd, London SE1 7EH, UK
bGuy’s and St Thomas’ NHS Foundation Trust, London, UK
*Correspondence: Matthew Cauldwell. Email: matthew.cauldwell@imperial.ac.uk

Key content
• Systemic lupus erythematosus (SLE) is an autoimmune condition that has multi-organ involvement.
• It is approximately ten times more common in women than in men and is often diagnosed during the childbearing years.
• SLE is known to increase the risk of spontaneous miscarriage; it can also cause fetal growth restriction and increased rates of sudden intrauterine death, pre-eclampsia and preterm delivery.
• Management of women with lupus nephritis can be difficult, as the disease may mimic and overlap significantly with pre-eclampsia.
• Multidisciplinary management of pregnant women with SLE ensures optimal surveillance of both mother and fetus.

Learning objectives
• To understand how to manage pregnant women with SLE.
• To understand the importance of pre-pregnancy counselling for women with SLE.
• To understand the features and associated risk factors which increase the chance of adverse pregnancy outcome in women with SLE.
• To understand which therapies for SLE can be used safely in pregnancy and while breastfeeding.
• To understand the role of the multidisciplinary team in the care of women with SLE, particularly those with underlying organ impairment.

Ethical issues
• When should women with SLE be advised against pregnancy?
• At what point should termination of pregnancy be considered if there is deterioration in maternal health in early pregnancy?

Keywords antiphospholipid syndrome / drug therapy / fetal growth restriction / perinatal complications / pre-conception counselling / pre-eclampsia / thromboembolism


Introduction
Systemic lupus erythematosus (SLE) is an idiopathic autoimmune condition which has multi-organ involvement. Diagnosis is based on both clinical manifestations and laboratory indices. The disease course can be sporadic and unpredictable but is typically characterised by periods of relapse and remission. This article discusses both the maternal and fetal complications of SLE and management of the disease during pregnancy.

Incidence
The literature quotes variable rates of SLE, which may be due to improvements in diagnostic testing. The American Rheumatism Association first devised a framework for SLE in 1971; this has had several subsequent revisions and the most recent is outlined in Box 1. The disease affects women and men in a ratio of 10:1. In the UK, population-based studies have shown that the disease tends to affect Afro-Caribbean people most frequently, followed by Asian people. The mean age of diagnosis also varies in the literature, but most women seem to be diagnosed during the childbearing years. The prevalence of SLE in women of childbearing years is around 1 in 500.

Pathophysiology
The exact cause of SLE remains unknown, but it has been proposed that an environmental trigger such as ultraviolet light or a viral infection; for example, the Epstein–Barr virus, combined with a genetic predisposition, forms the basis of the disease process. There is a 25% concordance for SLE among monozygotic twins.

The disease is characterised by immune complex deposition which causes inflammation in vascular beds. There is polyclonal B-cell activation which is thought to result in antinuclear antibody production. There is also an associated impairment of T-cell regulation and deficiencies in complement which leads to a failure to remove these immune complexes.
Box 1. 1997 update on 1982 American College of Rheumatology classification criteria for systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>Oral or nasopharyngeal ulceration, usually painless, observed by physician</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Non-erosive arthritis of two or more peripheral joints, with tenderness, swelling or effusion</td>
</tr>
<tr>
<td>Pleuritis or pericarditis</td>
<td>Pleuritis: convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion, or pleuritis: documented by electrocardiogram or rub or evidence of pericardial effusion</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Persistent proteinuria &gt;0.5 g per day or &gt;–3 if quantification not performed, or cellular casts: may be red cell, haemoglobin, granular, tubular, or mixed</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>Seizures: in the absence of offending drugs or known metabolic derangements; e.g. uraemia, ketoacidosis, or electrolyte imbalance, or psychosis: in the absence of offending drugs or known metabolic derangements, e.g. uraemia, ketoacidosis, or electrolyte imbalance</td>
</tr>
<tr>
<td>Haematological disorder</td>
<td>Haemolytic anaemia: with reticulocytosis, or leucopenia: &lt;4000/mm³ on ≥ 2 occasions, or lymphopenia: &lt;1500/mm³ on ≥ 2 occasions, or thrombocytopenia: &lt;100 000/mm³ in the absence of offending drugs</td>
</tr>
<tr>
<td>Immunological disorder</td>
<td>Anti-DNA: antibody to native DNA in abnormal titre, or anti-Sm: presence of antibody to Sm nuclear antigen, or positive finding of antiphospholipid antibodies on: (i) abnormal serum level of IgG or IgM anticytodiaphilin antibodies (ii) positive test result for lupus anticoagulant using a standard method, or (iii) false-positive test result for ≥ 6 months confirmed by Treponema pallidum immobilisation or fluorescent treponemal antibody absorption test</td>
</tr>
<tr>
<td>Positive antinuclear antibody</td>
<td>An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs</td>
</tr>
</tbody>
</table>

Any combination of four or more of 11 criteria, well documented at any time during a woman’s history, makes it likely that she has SLE (specificity and sensitivity are 95% and 75%, respectively).

Pre-pregnancy counselling

This should form the first part of management for women with an established diagnosis of SLE, as conception in a period of quiescence has been shown to reduce the likelihood of a flare of their disease during pregnancy. Fertility is not thought to be reduced in women with SLE unless there is concurrent ovarian failure associated with the use of high cumulative dosages of cyclophosphamide, particularly in older women, or unless there is end-stage renal failure (chronic kidney disease stage 5) associated with lupus nephritis, which can cause amenorrhoea. Non-steroidal anti-inflammatory drugs (NSAIDs) can cause infertility by means of inhibition of cyclooxygenase, which controls ovulation, known as luteinised unruptured follicle syndrome. Women who have been investigated for infertility without any obvious cause but who regularly take NSAIDs should be advised to stop taking these medications and use alternative analgesia, as fertility may resume.

During the pre-pregnancy consultation the woman should be assessed for disease activity and the presence of any organ-system involvement (Box 2). The presence of anti-Ro/La and antiphospholipid antibodies should also be determined. These antibodies are associated with congenital heart block and neonatal cutaneous lupus syndrome. Antiphospholipid antibodies are present in about 30% of women with SLE and are associated with arterial and venous thrombosis, recurrent miscarriage, fetal growth restriction, fetal loss and preterm delivery due to uteroplacental insufficiency; they require specific management.

Pre-pregnancy counselling should also include a discussion regarding medications (see Drug therapy in SLE).

Women should be counselled regarding the possible risks associated with SLE in pregnancy. They can be reassured that with quiescent disease, without associated antiphospholipid syndrome (APS), hypertension or renal involvement the risks of miscarriage/stillbirth and fetal growth restriction are not significantly increased compared with background rates and that adverse outcomes are more likely with the above complications. The risk of miscarriage and stillbirth in pregnancies complicated by lupus varies in the literature from 6–35% and from 0–22%, respectively.
Box 2. Investigations for assessment of disease activity in the pre-pregnancy consultation

<table>
<thead>
<tr>
<th>Organ/system</th>
<th>Complication/manifestation/investigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Pulmonary hypertension, valvular heart disease, cardiomyopathy: assess with echocardiography</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pulmonary fibrosis: may need to consider chest X-ray, CT, lung function tests if there is underlying restrictive respiratory involvement</td>
</tr>
<tr>
<td>Renal</td>
<td>Urine dipstick and protein:creatinine ratio to screen for and to quantify any underlying proteinuria. Document and quantify presence of haematuria, hypertension and/or renal impairment (lupus nephritis)</td>
</tr>
<tr>
<td>Renal function tests to assess pre-existing renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>Haematology/immunology</td>
<td>Thrombosis: assessment of risk and need for anticoagulation. Full blood count to determine any anaemia, neutropenia or thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Autoantibody profile: antiphospholipid (aPL), anticardiolipin (aCL), lupus anticoagulant (LA), anti-dsDNA and anti-Ro/anti-La antibodies, complement C3/C4 levels</td>
</tr>
</tbody>
</table>

CT = computed tomography

Obstetric management

It is important to appreciate that not all pregnancies in women with SLE need to be considered as high risk. Careful identification and stratification should take place to allow women to be managed on an individual basis. Women with quiescent skin and/or joint disease who have no other underlying organ impairment and who do not require multidrug therapy or an incremental increase in their current drug dosage are very different from those with a history of nephritis/hypertension or concurrent APS.

Pregnant women with active SLE/lupus nephritis or anti-Ro/La/antiphospholipid antibodies should be considered as a higher risk group and managed in centres with appropriate experience. Care should be carried out in a multidisciplinary setting where obstetricians/midwives and physicians/haematologists work closely together to optimise care. It is difficult to recommend precisely how often these women should be reviewed, but those with more active disease need closer monitoring and often require hospital admission. For those individuals with stable disease, 4-weekly reviews of disease activity and regular assessment of fetal growth, blood pressure and proteinuria are appropriate. For those at particular risk of fetal growth restriction and/or pre-eclampsia because of active disease or previous history, more frequent assessment is indicated.

For those women who are anti-Ro/La positive the fetal heart rate should be monitored and recorded at each visit and fetal echocardiography assessments made at 18–20 and ~28 weeks of gestation.

Careful obstetric management involves an awareness of the possibility of lupus flare and an understanding of how this can overlap with normal pregnancy-related changes and with pre-eclampsia. Pregnancy and SLE-related changes are summarised in Box 3.
Box 3. Comparison of pregnancy and SLE-related changes

<table>
<thead>
<tr>
<th>Features</th>
<th>Pregnancy-related</th>
<th>Lupus activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>Physiological haemodilution</td>
<td>Anaemia of chronic disease</td>
</tr>
<tr>
<td></td>
<td>Iron deficiency</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td>Pre-eclampsia</td>
<td>Nephritis</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Physiological increase of baseline proteinuria</td>
<td>Inflammatory synovitis</td>
</tr>
<tr>
<td></td>
<td>related to pregnancy or withdrawal of ACE inhibitors</td>
<td>APS</td>
</tr>
<tr>
<td>Joint swelling/pain</td>
<td>Mechanical arthralgia/effusion</td>
<td>Malar rash</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Gestational</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HELLP syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-eclampsia</td>
<td></td>
</tr>
<tr>
<td>Facial rash</td>
<td>Melasma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Facial blushing</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>Eclampsia</td>
<td></td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; HELLP = haemolysis, elevated liver enzymes, low platelet count; APS = antiphospholipid syndrome

Risk of thromboembolism
Women should be individually assessed for risk of thromboembolism. Ideally, this should be done at the earliest opportunity: it can be done as part of pre-pregnancy assessment and counselling. Risk of thromboembolism and the possible need for thromboprophylaxis should be reassessed in such circumstances as admission to hospital for a lupus flare.

Particular care is needed in women with concurrent APS, who have a higher risk of a thromboembolic event. Women who have had a previous venous thromboembolism (some of whom may be on long-term warfarin) should receive thromboprophylaxis with low molecular weight heparin throughout pregnancy and for 6 weeks postpartum or until converted back to warfarin.

Management of SLE flares
The risk of an SLE flare in pregnancy is increased with active disease in the 3–6 months prior to conception, with the majority of flares occurring in the second half of pregnancy. Most flares can be managed expectantly with medical management and adjustments to drug therapy (see ‘Drug therapy in SLE’). The blood pressure should be monitored closely to detect pregnancy-induced hypertension or pre-eclampsia and the woman should be screened for proteinuria, which should be quantified with either a urinary protein:creatinine ratio (PCR) or 24-hour urine collection.

Distinguishing pre-eclampsia from lupus nephritis
This is, perhaps, the most challenging aspect of obstetric management. The features of lupus nephritis include hypertension and proteinuria with or without haematuria and renal impairment. Lupus nephritis is caused by autoantibodies which produce immune complexes: these are deposited in the kidneys and they activate the complement cascade, causing a generalised inflammatory response. The presence of haematuria or red cell casts as well as a rise in anti-dsDNA titres or a fall in complement levels help to distinguish this from pre-eclampsia; in addition, lupus disease activity in non-renal organ systems suggests that a lupus nephritis flare is more likely. New-onset lupus nephritis without a previous history of renal involvement is unusual but not impossible.

Despite these distinguishing features the only definitive and reliable investigation that can be used to distinguish pre-eclampsia from lupus nephritis is renal biopsy. This is not generally undertaken during pregnancy because complications such as bleeding are greatly increased. It may be appropriate in the first or second trimester if it is felt that the result is likely to alter management; for example, if there is concern about underlying lupus nephritis, for which appropriate treatment with immunosuppressive agents may allow prolongation of the pregnancy. In cases of lupus nephritis that fail to respond to increasing dosages of steroids and azathioprine, and where there is a deterioration of renal function and/or hypertension, other immunosuppressive drugs may be considered, such as mycophenolate mofetil or tacrolimus. Such management decisions should be undertaken in consultation with nephrologists and rheumatologists, as there are associated risks (see Drug therapy in SLE).

Management of blood pressure in lupus nephritis should follow the same algorithm as for treatment of pregnancy-induced hypertension or pre-eclampsia. The blood pressure should ideally be kept below 140/90 mmHg.

Fetal management
SLE also confers greater risks to the fetus and there needs to be an awareness of the fetal problems that can develop. It is generally associated with increased rates of miscarriage, although what must be taken into account is that many women with SLE also have APS. However, it is generally thought that women with SLE without APS have an increased rate of miscarriage, possibly related to disease activity, and
they should be appropriately counselled regarding this in the pre-pregnancy period.

**Scanning and Doppler ultrasound**

There is no definitive guide stipulating the absolute timing of fetal scans and the frequency between scans in pregnancies complicated with SLE. It is important for the obstetrician to be aware of the risks of congenital heart block, fetal growth restriction and increased rates of preterm delivery and pre-eclampsia. These must all be taken into account when deciding whether increased fetal scanning is indicated. Scanning at least every 4 weeks to screen for fetal growth restriction in those women at risk is generally accepted and fetal echocardiography referral should be arranged for those with anti-Ro/La antibodies or if any cardiac abnormalities are detected on ultrasound scan.

Doppler studies can be used to estimate placental function and can be an aid to predicting outcomes such as pre-eclampsia and fetal distress. A uterine artery Doppler should be first carried out at 20 weeks and repeated 4 weeks later if any abnormality is found. A raised pulsatility index or diastolic notching are associated with increased risk for developing pre-eclampsia, as they can indicate underlying placental dysfunction. Nevertheless, not all women with an abnormal uterine artery Doppler will develop complications, so it is important not to treat abnormal Doppler in isolation. Second trimester Doppler has been shown to predict late pregnancy outcome in SLE and/or APS in some but not all studies.27

**Fetal growth restriction**

Since this is common in the context of pregnancies complicated by hypertension, APS and pre-eclampsia, it is not surprising that pregnant women with SLE are also at risk of fetal growth restriction. It may affect nearly one in four pregnancies with maternal SLE and has been reported as occurring in as many as 35%, particularly with concurrent lupus nephritis.28

**Congenital heart block**

This is associated with maternal anti-Ro/La autoantibodies. Antibodies cross the placenta and destroy the Purkinje system. The usual presentation is a fixed fetal bradycardia of 60–80 beats per minute on ultrasound scan. It occurs in 2–3% of fetuses of women with the anti-Ro/La antibody and there is a recurrence rate of 16% in subsequent pregnancies. It is associated with significant perinatal morbidity and mortality, with about half of infants requiring pacing by the first year of life. Congenital heart block develops between 18–28 weeks of gestation and fetal echocardiography should be performed around this period to detect it. Hydrops fetalis can occur in utero and is thought to be due to the degree of endomyocardial fibrosis and associated myocarditis.

**Neonatal lupus rash**

This forms part of the neonatal lupus erythematosus spectrum, manifesting as annular inflammatory lesions, which appear much like lesions of subacute cutaneous SLE. The lesions are most commonly seen on the face and scalp and appear typically after ultraviolet exposure in the first 2 weeks of life, but up to 3–6 months postpartum. The rash generally appears spontaneously and can persist for up to 6 months postnatally until the neonate clears the maternal antibodies. It is rare for neonatal cutaneous lupus and congenital heart block to occur together in the same individual. Skin biopsy shows histopathology and immunofluorescence typical of that of cutaneous lupus.

**Preterm delivery**

This is more common in pregnancies complicated by SLE and is often compounded by obstetric intervention and a tendency to deliver once the fetus is mature. Review of the literature suggests that the most common indication for delivery is pre-eclampsia, followed by fetal distress and fetal growth restriction. Premature rupture of membranes is also regarded as being more frequent in pregnancies complicated by SLE; rates vary and are generally quoted as ~20%. Interestingly, this risk does not appear to be related to disease status or serology, although women on steroid treatment appear to have a greater risk.32

**Drug therapy in SLE**

Box 4 lists the majority of the pharmacological agents used in the treatment of SLE, their mechanism of action, some of the contraindications to use and safety in pregnancy and breastfeeding. Drug therapy is an important consideration, as it is often necessary to manage women with a combination of different therapies. This is where the experience of clinicians who treat pregnant women with SLE on a regular basis is invaluable.

Glucocorticoids, mainly in the form of prednisolone, are frequently but not exclusively used as one of the first-line treatments in pregnancy. The dosage used does not vary greatly between pregnant and non-pregnant patients. The risk of adverse effects of steroids on the fetus is thought to be low, with little evidence for congenital malformations or neonatal adrenal suppression. Prednisolone, methylprednisolone and hydrocortisone are more efficiently metabolised by placental enzymes than dexamethasone and betamethasone and therefore cross the placenta in small amounts only. The adverse effects of steroids on the mother, however, are more numerous. These include weight gain, immunosuppression (and therefore increased risk of infections), acne, gastrointestinal irritation and, probably the most important adverse effect in pregnancy, increased glucose intolerance. Women on moderate to high dosages of steroids should therefore be screened regularly for gestational diabetes.33
### Box 4. Pharmacological agents used in the treatment of SLE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Placental transfer</th>
<th>Effects on fetus</th>
<th>Safety in pregnancy and breastfeeding</th>
<th>When to stop or to continue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory and immunosuppressive</td>
<td>Betamethasone and dexamethasone cross placenta readily. Prednisolone and hydrocortisone cross less well.</td>
<td>Long-term follow-up shows no significant neurodevelopmental delay.</td>
<td>May breastfeed safely as only small amounts found in breast milk.</td>
<td>Continue during pregnancy.</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Immunosuppressive agent—prevents cell proliferation and inhibits lymphocyte function.</td>
<td>Crosses placenta but fetal liver lacks enzyme to convert to active metabolite.</td>
<td>No cases of congenital abnormalities.</td>
<td>Safe in pregnancy and breastfeeding, but use at minimum effective dose.</td>
<td>Do not stop without guidance from rheumatology staff. Safe to continue.</td>
</tr>
<tr>
<td>Mycophenolate mofetil (MMF)</td>
<td>Inhibitor of purine synthesis.</td>
<td>Crosses placenta and is excreted in breast milk.</td>
<td></td>
<td></td>
<td>Stop (change to azathioprine) prior to conception but seek guidance from rheumatology staff.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent.</td>
<td>Crosses placenta and is excreted in breast milk.</td>
<td>Teratogenic. Increased rates of miscarriage and congenital abnormalities.</td>
<td>Excreted in breast milk, so should be avoided altogether in pregnancy.</td>
<td>Stop prior to conception but in a woman with flare consult rheumatology staff. Seek advice from rheumatology/nephrology staff regarding usage.</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>T-cell mediated response prevents formation of interleukin-2.</td>
<td>Crosses placenta and found in fetal blood.</td>
<td>Main problems reported: prematurity and low birthweight, but this may relate to underlying disease. Increase in congenital abnormalities.</td>
<td>Treatment used extensively in transplant patients and autoimmune disease. Breastfeeding probably safe.</td>
<td>Need advice from rheumatology/nephrology staff.</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Disrupts lysosome presentation and the processing of antigens.</td>
<td>Does cross placenta.</td>
<td>No increase in congenital abnormalities.</td>
<td>Withdrawal in non-pregnant patients may precipitate flare, so safe to continue. May breastfeed safely.</td>
<td>Continue throughout pregnancy, do not withdraw.</td>
</tr>
</tbody>
</table>

Other immunosuppressant agents that are frequently used and are generally considered safe during pregnancy include azathioprine and hydroxychloroquine. There is no indication to discontinue them during pregnancy.

It is also worth noting that several drugs can cause a lupus-like syndrome. The most common of these are hydralazine, procainamide, quinidine, isoniazid, diltiazem and minocycline. The pathophysiology of drug-induced lupus is not completely understood, but in the case of hydralazine it is thought to be caused by the formation of antinuclear antibodies to H1 and the H3–H4 complex (antihistone). However, these drugs do not cause disease flare in women with established lupus.
Postpartum care
This includes:

- ongoing management and treatment of any underlying pregnancy-induced hypertension
- a risk assessment and prophylaxis regimen for thrombosis, particularly in women with APS or who have a previous history of thrombosis or nephrotic syndrome
- advice regarding contraception and on avoiding estrogen-containing preparations, as these increase the risk of a flare
- vigilance concerning the increased risk of lupus flare in the postpartum period.

Conclusion
The management of SLE and pregnancy should be undertaken in a multidisciplinary setting. Labelling all pregnancies in women with SLE as high risk is not helpful or appropriate as those with quiescent disease will, in many cases, have uncomplicated pregnancies. For women who have active disease in pregnancy, are at risk of neonatal lupus or who have lupus nephritis or APS and therefore require closer monitoring because of increased risks of maternal and fetal adverse outcome, more intensive surveillance by an expert team is important. The involvement of obstetricians and physicians with experience of managing SLE in pregnancy improves the outcome for the mother and fetus.

References
27. Bramham K, Hunt BJ, Germain S, Calatayud I, Khamashita M, Bewley S, Nelson-Piercy C. Pregnancy outcome in different clinical phenotypes of...


