PREGNANCY PLUS

Systemic lupus erythematosus

Lucy H Mackillop,¹ Sarah J Germain,² Catherine Nelson-Piercy³

¹Queen Charlotte's and Chelsea Hospital, London W12 0HS

²St Thomas' Hospital, London SE17EH

³Queen Charlotte's and Chelsea Hospital and St Thomas' Hospital, London

lucymackillop@hotmail.com

BMJ 2007;335:933-6

doi: 10.1136/bmj.39358.519491.AD

Systemic lupus erythematosus in pregnancy brings risks for the mother, and possible harm to the fetus if the disease is treated. This article discusses the challenges of management

Systemic lupus erythematosus (SLE) is a multisystem relapsing and remitting autoimmune disease. The management of this condition in pregnancy provides the obstetrician, physician, and general practitioner with particular challenges and concerns related to the mother and her baby (see scenario box).

How common is SLE?

The condition is much more common in women than men (9:1), with peak onset during childbearing years.¹ A recent extensive review of published epidemiology studies showed that the prevalence ranges from 0.07 per 1000 in white Americans to 1.59 per 1000 in British Afro-Caribbeans.^{w1}

How does pregnancy affect SLE?

Several case studies suggest that pregnancy exacerbates SLE and increases the likelihood of a flare antenatally or in the puerperium.^{2 w2} In one prospective case-control study 65% of patients with SLE who were pregnant had a flare compared with 42% of those who

Box 1 | Diagnostic criteria for the antiphospholipid syndrome^{w7}

Antiphospholipid antibodies plus at least one of the following:

- Arterial or venous thrombosis
- Three or more miscarriages (at <10 weeks' gestation)
- Fetal death (at >10 weeks' gestation with normal fetal morphology)
- Premature birth (at <34 weeks' gestation with normal fetal morphology) as a result of pre-eclampsia or severe placental insufficiency

were not pregnant during the same time period.³ The type of flare usually follows previous patterns. The postpartum period is also a time of susceptibility to developing autoimmune disorders.^{w3}

Renal involvement is one of the more serious complications of SLE, and, as with all types of renal disease, there is a risk of deterioration of renal function in pregnancy, particularly in patients with hypertension, heavy proteinuria, and high baseline serum creatinine concentration.^{w4 w5} A recent meta-analysis reported that renal impairment occurred in 3-27% of cases of lupus nephritis flare; in 0-10% of these cases it was irreversible.^{4 5} Nephritis in SLE may also present for the first time during pregnancy but can be difficult to diagnose.

With the physiological changes in clotting factors in pregnancy (see a previous article in the *BMJ* Pregnancy Plus series⁶), women with SLE are at particular risk of maternal thrombosis (venous and arterial), especially in the puerperium, and thrombosis is usually associated with the presence of antiphospholipid antibodies.⁷

How does SLE affect pregnancy?

SLE may affect the health of the mother or her baby. SLE does not usually affect fertility (although its treatment may), but it is associated with increased risks of early miscarriage, intrauterine fetal death, pre-eclampsia, intrauterine growth restriction, and preterm delivery.^{2 8}

Thirty to forty per cent of women with SLE have antiphospholipid antibodies (including anticardiolipin antibodies or lupus anticoagulant).^{w6} The combination of antiphospholipid antibodies and one or more of the characteristic clinical features (box 1) is known as the antiphospholipid syndrome. In a prospective study of

This is one of a series of occasional articles about how to manage a pre-existing medical condition during pregnancy. If you would like to suggest a topic for this series please email Amy Davis (adavis@bmj.com). References w1-w30 are on bmj.com

Scenario

A 30 year old woman is referred to the obstetric medicine clinic. She is eight weeks pregnant according to the timing of her last menstrual period. She has systemic lupus erythematosus (SLE), diagnosed in 1998. The disease has affected predominantly her joints, but she did have a related nephritis flare in 2000. She has never had a venous or arterial thromboembolus. Her last SLE flare was three years ago during her last pregnancy, and it was confined to her joints; her baby daughter then (now 3 years old) had been delivered normally after induction of labour at 36 weeks' gestation. She had gestational diabetes from 24 weeks in her last pregnancy, but an oral glucose tolerance test six weeks postnatally was normal, confirming true gestational diabetes.

Her current medications include azathioprine 125 mg once daily, prednisolone 4 mg once daily, hydroxychloroquine 200 mg twice daily, and aspirin 75 mg once daily. She is feeling well, with no joint pains. Her blood pressure is 115/65 mm Hg, urine analysis was negative for blood and protein, and an oral glucose tolerance test was normal. Her latest serology shows that she is positive for antinuclear antibodies, negative for double stranded DNA (although this has been positive in the past), positive for anticardiolipin antibody IgG, positive for anti-Ro antibody, and her complement 3 and 4 levels are in the normal range. Renal function is normal (serum creatinine concentration 67 µmol/l).

Box 2 | Factors increasing adverse outcome in pregnancy

- Disease activity
- Hypertension
- Renal involvement
- Antiphospholipid antibodies
- Anti-Ro or anti-La antibodies

267 pregnancies in 203 patients with SLE, live birth rate was 86% (incidence of prematurity 31%, small for gestational age 23%). Most of the fetal losses were in women with associated antiphospholipid antibodies.⁹

Pregnancy outcome is particularly affected by renal disease. Even quiescent renal lupus is associated with increased risk of fetal loss, pre-eclampsia, intrauterine growth restriction, and premature delivery, particularly if there is hypertension or proteinuria.⁴ Pulmonary hypertension, reported in up to 14% of patients with lupus, is associated with a high risk of maternal death.^{w8} Conversely, for women with SLE in remission and without hypertension, renal involvement, or the antiphospholipid syndrome, the risk of problems in pregnancy is no higher than in the general population.^{4 w9}

Antibodies to extractable nuclear antigens, particularly anti-Ro and anti-La antibodies, may be present in women with SLE. However, these antibodies may also be present in asymptomatic women or in those with Sjögren's syndrome, where they are associated with a characteristic photosensitive rash. The neonate may be affected by transplacental passage of these antibodies. Cutaneous neonatal lupus is the most common manifestation of neonatal lupus, occurring in the newborns of up to 16% of women with these antibodies in one prospective study.^{w10} It presents with a characteristic rash (figure) at about 2 weeks of life. Congenital heart block is the most serious manifestation and may present as early as 16 weeks' gestation. It affects about 2% of mothers with anti-Ro or anti-La antibodies and may lead to fetal demise.^{w11 w12} The risk of congenital heart block increases to 15-20% if one child has been affected and to 50% if two children are affected.

Box 2 summarises the disease factors that increase the likelihood of adverse outcome in pregnancy.

How do you manage SLE in pregnancy?

Pregnancy care is best given in multidisciplinary clinics where physicians and obstetricians can regularly monitor disease activity and markers of fetal wellbeing.

Preconception counselling

Knowledge of renal function, blood pressure, and the presence and titres of anti-Ro or anti-La antibodies and antiphospholipid antibodies allows prediction of the risks to the woman and her baby. An extensive meta-analysis has shown that the outlook is better if conception occurs during remission.^{w13} Case-control studies in women with lupus nephritis suggest that avoidance of pregnancy for at least six months after a flare improves outcome,⁴ and expert opinion suggests a similar time period for stabilisation of any preconception drug changes.

Maternal surveillance

Several baseline investigations should be done in early pregnancy (box 3). Medication should be optimised, and in women with the antiphospholipid syndrome the decision to start aspirin and/or heparin can be made¹⁰; evidence exists that these anticoagulants improve fetal outcome,^{w14} and thromboprophylaxis is essential in

Table 1 | Differentiating between pre-eclampsia and renal SLE flares

Investigations to help differentiate	Result in pre-eclampsia	Result in renal SLE flare
Hypertension	Present	Present
Proteinuria	Present	Present
Platelets	Low	Low
Creatinine	Raised	Raised
Liver function tests	Normal or raised	Normal
Anti-DNA antibodies	No rise	Increased
Complement 3 and 4	Normal or raised	Low
Urine analysis	Protein	Protein, blood, and cellular casts

SLE= systemic lupus erythematosus.

women who have the antiphospholipid syndrome and have had previous thromboembolism. Both aspirin and heparin are safe in pregnancy. Heparin does not cross the placenta, and maternal heparin induced thrombocytopenia and osteopenia are extremely rare in pregnancy when low molecular weight heparin is used.^{w15}

Regular follow-up to monitor serological disease markers (full blood count, double stranded DNA, complement 3 and 4), maternal symptoms, blood pressure, and urine analysis will be needed, with frequency dependent on disease activity. Delivery method can be based on obstetric indications. Decision on timing of delivery depends on disease activity and maternal and fetal health and is made on a case by case basis.

Fetal surveillance

In addition to a detailed morphology scan at 20 weeks, regular growth scans (typically at 28, 32, and 36 weeks) should be done—especially in women with hypertension, renal disease, or the antiphospholipid syndrome—to look at fetal growth and markers of fetal wellbeing. In women with anti-Ro or anti-La antibodies, fetal echocardiography may be offered at 18 weeks and again in the third trimester to identify any cardiac conduction abnormalities.

What if the disease flares up in pregnancy?

SLE flares may be difficult to diagnose during pregnancy as many clinical features of flares are common to pregnancy too (box 4). Differentiation of active renal lupus from pre-eclampsia is notoriously difficult, and the two conditions may occur together (table 1). In addition, an increasing degree of proteinuria may be the result of normal physiological changes during pregnancy or the withdrawal of angiotensin converting enzyme inhibitors.

It is important to diagnose a flare as it must be appropriately and aggressively managed to minimise maternal and fetal morbidity. Management includes analgesics for joint pain, immunosuppression for more severe disease, and intensive surveillance of the mother and the fetus.

Evidence conflicts as to whether corticosteroids prevent flares.⁴ Current expert opinion suggests that prescribing prophylactic steroids is not indicated.²

Box 3 | Baseline investigations

- Full blood count
- Urea, creatinine, electrolytes
- Liver function tests
- Serology (antinuclear antibodies, double stranded DNA, anti-Ro/anti-La antibodies, antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulant), complement 3 and 4
- Blood pressure
- Urine analysis (and quantification of protein, if present)

Table 2 | Evidence for adverse effects of immunosuppressants used in pregnancy and breast feeding (adapted from review by Ostensen ¹¹)

Drug	Evidence	Whether drug can be used	
		In pregnancy	In breast feeding
Hydroxychloroquine and chloroquine	No increased risk of miscarriage, congenital malformation, or stillbirth at doses used in rheumatic diseases (for example, hydroxychloroquine 200-400 mg/day). Cessation increases risk of flare, and a long half life means that stopping does not prevent fetal exposure.	Yes	Yes
Azathioprine	Fetus lacks enzyme to convert to active form. Fetal and neonatal immunosuppression is minimal if dose is <2 mg/kg and maternal white cell count is normal.	Yes	Yes ^{w29}
Ciclosporin	No increase in congenital malformations. Trend towards prematurity and intrauterine growth restriction is not significant and probably related to more severe maternal disease. Small amounts in breast milk, but no adverse effects reported.	Yes	If benefits outweigh potential risks
Tacrolimus	No increase in congenital malformations. Increased rates of prematurity related to severity of maternal disease. In one case report, a baby received maximum of 0.02% of maternal dose via breast milk.	Yes	Yes, with caution
Intravenous immunoglobulins	These cross the placenta after 32 weeks but with no adverse effects to fetus.	Yes	Yes
Mycophenolate mofetil	Increased risk of congenital abnormalities. ^{w30} Enterohepatic recirculation and a long half life.	No (stop six weeks before conception)	No
Cyclophosphamide	Alkylating agent. Teratogenic and fetotoxic. Risk of suppression of neonatal haematopoiesis.	No (stop three months before conception)	No
Methotrexate	Folate antagonist. Teratogenic and fetotoxic.	No (stop three months before conception, and give folic acid 5 mg daily periconceptually and throughout pregnancy)	No
Leflunomide	Congenital abnormalities in animal studies, and human studies are limited. A long half life of active metabolites.	No (use cholestyramine to increase clearance preconception)	No
Biological agents (such as etanercept, infliximab, adalimumab, rituximab)	Limited experience in human pregnancies and breast feeding, but no adverse fetal or neonatal outcomes to date.	Limit to severe disease	Probably avoid

Box 4 | Clinical features common to systemic lupus erythematosus and pregnancy

- Hair loss
- Oedema
- Facial erythema
- Fatigue
- Anaemia
- Raised erythrocyte sedimentation rate
- Musculoskeletal pain

Analgesics and non-steroidal anti-inflammatory drugs

Arthralgia is a common symptom in SLE. Paracetamol is usually the first line analgesic as no adverse effects are known to occur in pregnancy.^{w16} Aspirin and non-steroidal anti-inflammatory drugs are not teratogenic,^{w17} but salicylates (in analgesic doses) and non-steroidal anti-inflammatory drugs may increase the risk of neonatal haemorrhage via inhibition of platelet function.^{w18} Non-steroidal anti-inflammatory drugs may be fetotoxic and lead to oligohydramnios via effects on the fetal kidney^{w19} and may cause premature closure of the ductus arteriosus.^{w20} Such drugs are therefore usually avoided in pregnancy, especially in the last trimester. Although codeine based analgesics are not the most effective analgesics for joint pain, they are safe in pregnancy.^{w21}

Immunosuppressants

Most women with a more severe SLE flare will require immunosuppression. Corticosteroids are the drugs of choice for fast relief of symptoms and disease control, and they may be continued or started during pregnancy. Prednisolone is metabolised by the placenta, and very little (10%) active drug reaches the fetus.^{w22} Corticosteroids have been associated with a small increase in the incidence of oral cleft,^{w23} intrauterine growth restriction,^{w24} and premature rupture of membranes.^{w25}

However, a recent large nationwide cohort study recorded no increased risk of congenital malformations and preterm birth in those women receiving corticosteroids,^{w26} and a small prospective study showed no increase in intrauterine growth restriction and no difference in infant behaviour and stress induced corti-

sol levels compared with controls.^{w27} The more recent data are reassuring, and expert opinion suggests that corticosteroids, and particularly prednisolone, are safe for the fetus. Maternal complications of steroids include an increased risk of gestational diabetes, hypertension, infection, and osteoporosis.¹¹

If a woman is taking long term maintenance steroids (>7.5 mg prednisolone a day for more than two weeks), parenteral steroids should be administered to cover the stress of labour and delivery. Prednisolone is safe in breastfeeding mothers as less than 10% of the active drug is secreted into breast milk.^{w28}

Table 2 lists other immunosuppressants and outlines the evidence for their use in pregnancy and breast feeding.

The case

Our patient (see scenario box at the start of this article) continued with her preconception medication, and folic

Cutaneous neonatal lupus

acid was added. She had a scan at 20 weeks that showed normal morphology and growth. At 18 and 32 weeks, fetal echocardiography was normal. At 22 weeks she developed severe arthralgia and lethargy, and her serology indicated an SLE flare (increasing double stranded DNA titres and falling levels of complement 3 and 4). She required 40 mg of prednisolone for symptom control. However, home blood glucose monitoring showed a raised blood glucose concentration, and gestational diabetes was confirmed with an oral glucose tolerance test. She required insulin four times a day in a basal bolus regimen until delivery. Prednisolone was reduced slowly to a 20 mg maintenance dose once daily.

Repeat growth scans were adequate, and labour was induced at 38 weeks for worsening arthralgia and hypertension. Urine analysis remained negative. A 2.5 kg live female infant was delivered vaginally, and the patient was discharged on day 3. The postnatal period was uncomplicated, and the mother breast fed her infant. She stopped insulin immediately after delivery, and antihypertensives were stopped 10 days later. Prophylactic low molecular weight heparin was prescribed postpartum for six weeks in view of the presence of anticardiolipin antibodies and SLE flare. Prednisolone was slowly reduced to 4 mg daily over three months.

Conclusion

Systemic lupus erythematosus and the overlap condition of the antiphospholipid syndrome present several challenges in managing a pregnant woman and her

fetus. A successful pregnancy outcome depends on stratification of risk at the outset (ideally before pregnancy) and careful and appropriate monitoring during the pregnancy. Should the disease flare up, aggressive but considered management is advocated to reduce maternal and fetal morbidity.

Contributors: LHM had the idea for the article. LHM and SJG prepared the first draft and did the literature search. LHM and CN-P managed the patient, together with Andrew McCarthy and Liz Lightstone. All authors contributed to further revisions of the article. CN-P will act as guarantor.

Competing interests: None declared.

Provenance and peer review: Commissioned, externally peer reviewed.

- 1 D'Cruz DP, Khamashta MA, Hughes GRV. Systemic lupus erythematosus. *Lancet* 2007;369:587-96.
- 2 Khamashta MA. Systemic lupus erythematosus and pregnancy. *Best Pract Res Clin Rheumatol* 2006;20:685-94.
- 3 Ruiz-Irastorza G, Lima F, Alves J, Khamashta MA, Simpson J, Hughes GR, et al. Increased rate of lupus flare during pregnancy and the puerperium: a prospective study of 78 pregnancies. *Br J Rheumatol* 1996;35:133-8.
- 4 Moroni G, Ponticelli C. The risk of pregnancy in patients with lupus nephritis. *J Nephrol* 2003;16:161-7.
- 5 Stratta P, Canavese C, Quaglia M. Pregnancy in patients with kidney disease. *J Nephrol* 2006;19:135-43.
- 6 Lim W, Eikelboom JW, Ginsberg JS. Inherited thrombophilia and pregnancy associated venous thromboembolism. *BMJ* 2007;334:1318-21.
- 7 Ware Branch D, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. *Obstet Gynecol* 2003;10:1333-44.
- 8 D'Cruz DP. Systemic lupus erythematosus. *BMJ* 2006;332:890-4.
- 9 Clowse MEB, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum* 2005;52:514-21.
- 10 Derksen RHW, Khamashta MA, Ware Branch D. Management of the obstetric antiphospholipid syndrome. *Arthritis Rheum* 2004;50:1028-39.
- 11 Ostensen M, Khamashta M, Lockshin M, Parke A, Brucato A, Carp H, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Research & Therapy* 2006;8:209-27.

LESSON OF THE WEEK

Anal ulceration induced by nicorandil

Fayyaz Akbar, Andrew Maw, Arnab Bhowmick

Department of General Surgery,
Glan Clwyd Hospital, Rhyl LL18 5UJ
Andrew.Maw@cd-tr.wales.nhs.uk
Accepted: 5 April 2007

In patients with anal fissures or anal ulceration, treatment with the drug nicorandil should be considered as a possible cause

Nicorandil is widely used to treat angina, particularly in patients with severe coronary vessel disease. Anal ulceration is a recognised side effect of its use,^{1 2} but the association between the two is not widely appreciated. We want to alert primary care practitioners, general physicians, dermatologists, cardiologists, and surgeons who may encounter such cases of the importance of this association.

Case report

A 73 year old man was referred to our department with a one year history of rectal bleeding, mucus discharge, and anal pain. Associated conditions included diabetes mellitus, hypertension, hypercholesterolaemia, and severe

ischaemic heart disease. Despite two previous coronary artery bypass operations, he continued to have angina. His medication included aspirin, atenolol, amlodipine, simvastatin, allopurinol, gliclazide, and 30 mg nicorandil twice a day.

Initial assessment found a small posterior anal fissure and anal skin tags. For investigation of the bleeding, he underwent a rigid sigmoidoscopy and a barium enema, results of which were normal. We made a provisional diagnosis of an uncomplicated idiopathic anal fissure and started him on conservative treatment with topical analgesics and laxatives.

His symptoms worsened, however, with increasing mucus discharge. Examination under anaesthesia showed normal rectal mucosa. There was a huge posterior anal fissure (2-3 cm wide) extending the entire length of the anal canal and another anterior fissure 1.0-1.5 cm wide with a flat base. The margins of the fissures were soft and non-indurated. We considered a diagnosis of Crohn's disease or malignancy, but

BMJ 2007;335:936-7
doi: 10.1136/bmj.39246.714896.BE