Lupus and pregnancy: integrating clues from the bench and bedside

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ABSTRACT

Adequate pregnancy care of women with systemic lupus erythematosus (SLE) rests on three pillars: a coordinated medical-obstetrical care, an agreed and well-defined management protocol and a good neonatal unit. Pregnancy should be planned following a preconceptional visit for counselling. Women with severe active disease or a high degree of irreversible damage, such as those with symptomatic pulmonary hypertension, heart failure, severe restrictive pulmonary disease or severe chronic renal failure should best avoid pregnancy. Treatment is based on hydroxychloroquine, low-dose steroids and azathioprine. Patients with antiphospholipid antibodies/syndrome should receive low-dose aspirin +/− low molecular weight heparin. The addition and the dose of heparin depend on the clinical profile of the patient, i.e. a previous history of miscarriage, foetal loss, placental insufficiency or thrombosis. A close surveillance, with monitoring of blood pressure, proteinuria and placental blood flow by Doppler studies helps the early diagnosis and treatment of complications such as preeclampsia and foetal distress. Postpartum follow-up is important.

Keywords Anticardiolipin, foetal death, lupus anticoagulant, miscarriage, preeclampsia, systemic lupus erythematosus.

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Systemic lupus erythematosus (SLE) is a complex disease with a strong feminine predilection, affecting as many as 1 in 1000 women in fertile age [1]. A normal consequence of the epidemiology of lupus is therefore the frequent interaction with pregnancy. Doctors looking after women with SLE must be prepared to give adequate counselling, planning and care before, during and after pregnancy. Fortunately, multidisciplinary units integrating medical specialists in autoimmune diseases, obstetricians and even haematologists and nephrologists are becoming common. They can assure the correct and coordinated management of pregnancy in women with lupus as well as of lupus during pregnancy.

Research in SLE pregnancy is not easy to perform. Most data come from observational studies, summarising the valuable experience of clinical units working in this field. Randomized controlled trials are notably scarce in this area, with the relative exception of antiphospholipid syndrome (APS). However, even in this condition, the quality of the studies is greatly limited by biases relative to the selection of patients. Thus, recommendations regarding the management of pregnant women with lupus must always be taken with caution. However, the great improvement in the foetal and maternal prognosis of lupus

pregnancies support the validity of clinical observations made by experienced teams [2].

Are women with lupus subject to complicated pregnancies?

A large number of complications can occur to pregnant women with SLE. Lupus may flare [3], residual renal impairment may worsen [4], hypertension or preeclampsia may develop and thrombosis, miscarriage, growth restriction and prematurity may be an issue [5]. Recent data from a national study in the US confirm those fears [6]. A total of 13 555 deliveries between 2000 and 2003, in women with a diagnosis of SLE at discharge, were identified. Women with a diagnosis of lupus were more likely than the general population to suffer from pregestational diabetes mellitus, hypertension, pulmonary hypertension, renal failure and thrombophilia (mainly APS). The chance of suffering pregnancy complications was 2- to 4-fold higher: preeclampsia happened in 22·5% of women with lupus, vs. 7·6% in the general population, preterm labour in 20·8% vs. 8·1% and intrauterine growth restriction in 5·6% vs. 1·5%, respectively. Moreover, medical complications such as stroke,

pulmonary embolism, deep vein thrombosis, major infections, bleeding and thrombocytopenia were 2–8 times more frequent among women with SLE.

Specific complications have been linked to certain clinical and/or immunological profiles. The clearest example is neonatal lupus syndromes (NNS) and anti-Ro/anti-La positivity [7]. Antiphospholipid antibodies (aPL) have been associated with a wide range of potential complications during pregnancy, including miscarriage, foetal death, intrauterine growth restriction, prematurity and preeclampsia [8]. Likewise, women with lupus nephritis are subject to a number of both medical and obstetric problems [4]. All these situations will be covered in ensuing sections.

Seventy-six per cent of the 63 women from the LUMINA cohort who got pregnant during the follow-up presented complications [9]. Moreover, these authors reported a significant, albeit modest, increase in irreversible damage postpartum, which was especially determined by disease activity and the presence of damage before conception. However, treatment-related variables were not entered in the model. In other studies, corticosteroid use, as well as disease activity, has been associated with prematurity and general adverse pregnancy outcome [10,11].

High-risk situations in lupus pregnancy

Lupus flare
Whether pregnancy increase lupus activity has been a question of debate for years. Now, it is generally agreed that SLE is more likely to flare in unselected women [3,12]. However, women with lupus in long-standing remission are much more likely to complete pregnancies uneventful from the lupus point of view [13,14]. Flares during pregnancy are usually not severe; though, data from the Hopkins Lupus Cohort showed an increased chance for developing lupus nephritis [15]. Demographic features, including social and racial, may certainly play a role in the conflicting results obtained by different investigators. One of the recently identified factors that increases the risk for lupus flares during pregnancy is hydroxychloroquine discontinuation. In a small randomised controlled trial, Levy et al.[16] showed that women taking hydroxychloroquine during pregnancy had lower activity scores and lower doses of prednisone at delivery. Clowse et al.[17] obtained similar results in a prospective cohort study, in which women not taking hydroxychloroquine, and, specially, those who had withdrawn it had more flares, higher activity scores and needed higher doses of prednisone.

Lupus flares are a problem not only for the mother. The impact of lupus activity on pregnancy outcome has been recently addressed by Clowse et al.[18]. Women with high lupus activity during pregnancy had a higher chance of miscarriage, prematurity and perinatal death [18]. In addition, increasing doses of prednisone used to treat flares may contribute to complications, and many other drugs are contraindicated during this period, making treatment much more problematic.

Clinical and immunological features of lupus activity may be difficult to recognise during pregnancy. Fatigue and mild arthralgia are common among normal pregnant women. Oedema normally appears during the last phases of pregnancy and, if symmetrical and in the absence of hypertension and/or proteinuria, is not a warning sign. Mild anaemia and thrombocytopenia are also common in pregnant women. Taking into account these particularities, lupus activity scales specific for pregnancy have been established [19,20]. However, in daily practice, experienced clinical judgement is the best way to evaluate lupus activity during pregnancy.

Lupus nephritis
Lupus nephritis is a clinical challenge, also – and specially – during pregnancy. The risk of suffering a renal flare seems variable, particularly related to SLE status at the time of conception and the history of previous renal involvement. Therefore, patients with recent active nephritis are at the highest risk, whilst those in long-standing remission with no past kidney disease are at the lowest [4].

A second important point is the recognition of renal activity during pregnancy. Urinary protein excretion normally rises during pregnancy in women with residual proteinuria, thus not always reflecting active disease [4]. Complement levels normally increase during pregnancy, a fact that limits their utility as markers of active lupus. Proteinuria, hypertension and decline in renal function can also be seen in preeclampsia; in fact, the differential diagnosis between these two conditions is difficult, even they can coexist, because women with renal disease are at a higher risk for hypertensive complications during pregnancy, including toxaemia [21]. Rising uric acid levels point to preeclampsia, whilst the presence of haematuria and/or cellular casts, extrarenal activity, rising anti-DNA antibody levels and falling complement levels (even within normal limits for nonpregnant patients) point to lupus nephritis [21]. Supporting therapy and labour induction in severe cases is commonly indicated.

Management of active lupus nephritis is also conflicting during pregnancy. Most immunosuppressive drugs, with the exception of azathioprine and cyclosporin, are contraindicated during pregnancy [22], making it difficult to treat proliferative forms. Antiproteinuric drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists cannot be used during the full pregnancy because of the risk of renal failure and oligoamnios [4]. Thus, a pulse steroid followed by a combination of prednisone (aiming for a rapid reduction to

maintenance doses < 7·5 mg d^{-1}) hydroxychloroquine and azathioprine is the usual therapy [5]. Intravenous immunoglobulins can be safely used in pregnant women [22] and are thus an option in active cases to buy time before labour induction can be performed.

The last issue is the impact of renal disease on pregnancy outcome. A recent study from the Toronto Lupus Cohort compared the course of 81 women with lupus renal involvement, suffered within 6 months preconception and delivery, and 112 without [23]. They only found a significant increase in the frequency of hypertension and a lower mean weight at birth in the group of patients with renal disease. On the other hand, complications such as preeclampsia or perinatal death were infrequent in both groups. A live baby was the result of almost 60% of pregnancies overall, without significant differences between women with or without nephritis.

However, these results are not in full agreement with those from other studies. A smaller retrospective study from Saudi Arabia, analysing the course of pregnancy among women with lupus nephritis, found a significantly higher frequency of pregnancy complications among those women with active disease, when compared with those in remission (foetal loss 52% vs. 30%, complicated premature deliveries, 36 vs. 16%, respectively) [24]. An observational study by Imbasciati *et al.* including 113 pregnancies in 81 women with lupus renal disease identified hypocomplementemia and the combined variable proteinuria > 1 gr d^{-1} or glomerular filtration rate below ml min^{-1} per 1·73 m^2 as independent predictors of adverse foetal or maternal outcomes [25]. Of note, treatment with low-dose aspirin was associated with an improvement in pregnancy outcome in this series. In line with this results, a recent review by Germain and Nelson-Piercy identified women with baseline serum creatinine levels higher than 2·5–2·8 mg dL^{-1} (220–250 μmol l^{-1}) as those most likely to suffer postpartum renal function decline as well as complications during pregnancy [26]. Finally, a recently published systematic review and meta-analysis found that lupus women with past or active nephritis are more likely to suffer hypertension and prematurity, those with a history of nephritis having also a higher risk for preeclampsia [27].

In view of these data, lupus renal disease does not generally preclude pregnancy. However, women with either active disease or established severe renal impairment and/or proteinuria should be monitored carefully, in view of the high chance of both maternal and foetal complications. Low-dose aspirin is useful in patients with a history of renal disease, because of its effect in preventing preeclampsia in high-risk pregnancies.

Preeclampsia
Apart from renal disease, a recent systematic review has identified several predictors of preeclampsia, such as a previous history of preeclampsia (odds ratio 7·19) and the presence of APS (odds ratio 9·72) [28]. Preeclampsia has no effective therapy other than delivery. Thus, prevention is the main goal. A recent meta-analysis has shown a statistically significant reduction in the frequency of pregnancy complications among women at high risk for preeclampsia who took low-dose aspirin [29]. Recurrent preeclampsia, preterm delivery < 34 weeks, perinatal death, small babies at birth and any serious adverse outcome were all significantly reduced by around 10%. Extrapolating these data to patients with SLE, treatment with low-dose aspirin during pregnancy would be indicated in women with aPL, history of preeclampsia, hypertension and/or renal disease.

Antiphospholipid syndrome
The presence of aPL is one of the most important predictors of adverse pregnancy outcome, both in women with and without SLE. A recent survey of 141 286 women delivering in Florida in 2001 has found positivity for aPL in 88 of them [30]. This subgroup was more likely to have preeclampsia/eclampsia (adjusted OR 2·3), placental insufficiency (adjusted OR 4·53) and a longer duration of admission (adjusted OR 3·93). Similar data come from Japan [31]. Women with positive aPL were at a higher risk for hypertension, preeclampsia, foetal death, growth restriction and prematurity. Combined positivity for both anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) multiplied the risk. Triple aPL positivity (LA plus aCL plus anti-β2-glycoprotein I) was also associated with prematurity and lower birth weight in an Italian study [32], as was the history of maternal thrombosis. In keeping with these data, a recent study from London also showed a worse obstetric profile in women with previous thrombosis [33]. Thus, aPL positivity is a risk marker for pregnancy complications, this risk being modulated by both immunological (the most number of positive aPL, the worst) and clinical profiles (women with previous thrombosis are at the highest risk).

Low-dose aspirin should be taken by all women with aPL to decrease the risk of miscarriage [34] and preeclampsia [29,34]. Preconceptional treatment has improved results in some series [35]. As warfarin is contraindicated during organogenesis and complicated to use afterwards, because of an increased risk of foetal bleeding [22], full anti-thrombotic-dose heparin, preferably low molecular weight, is given to women with previous thrombosis. For women without thrombosis, treatment should be individualised (Table 1). There is general agreement in treating those with foetal (late) deaths with aspirin plus low-dose heparin, although most data for this subgroup come from observational studies [34,36]. On the other hand, according to some clinical trials, some women suffering early miscarriages only may do well with low-dose aspirin alone [34], although current guidelines recommend the universal combination of

Table 1 Suggested regimens for the treatment of antiphospholipid syndrome in pregnancy

Antiphospholipid syndrome without prior thrombosis
a) Recurrent early (pre-embryonic or embryonic) miscarriage
Low-dose aspirin ALONE OR PLUS:
LMWH: usual prophylactic doses (e.g., enoxaparin 40 mg d^{-1} sc. or dalteparin 5000 U d^{-1}, sc.)
b) Foetal death (> 10 weeks gestation) or prior early delivery (< 34 weeks gestation) caused by severe preeclampsia or placental insufficiency
Low-dose aspirin PLUS:
LMWH: usual prophylactic doses (e.g., enoxaparin 40 mg d^{-1} sc. or dalteparin 5000 U d^{-1}, sc.)
Antiphospholipid syndrome with thrombosis
Low-dose aspirin PLUS:
LMWH: usual therapeutic dose (e.g., enoxaparin 1 mg kg^{-1} sc. or dalteparin 100 U kg^{-1}, sc. every 12 h or enoxaparin 1·5 mg kg^{-1} per d sc. or dalteparin 200 U kg^{-1} per day sc.)

aspirin and heparin [36]. In all cases, women should be informed of the different treatment possibilities, and the final option be assumed by the patient, the physician and the obstetrician. Adequate postpartum thromboprophylaxis with low-dose low–molecular weight heparin is important in all women with aPL, although the duration is a matter of debate. Four to six weeks is the usual recommendation [36]; however, recent consensus documents advocate shorter courses [37].

Neonatal lupus and congenital heart block

Neonatal lupus syndromes (NNS) is a rare complication affecting children born to mothers with lupus, Sjögren's syndrome and, less often, other autoimmune diseases, whose most serious form of presentation is congenital heart block (CHB). This syndrome is closely related to the presence of maternal anti-Ro and anti-La antibodies. These antibodies gain access to the foetal circulation during the active transport of IgG across the placenta that happens between the 16th and 30th weeks of gestation. The prevalence of CHB among newborns of anti-Ro-positive women with known connective tissue diseases is around 2% [38]. However, this risk increases to 18% in younger siblings of an infant with CHB [7]. The actual prevalence may be even higher, because incomplete forms of CHB have been described, including first-degree heart block that can progress during childhood [7]. Most children affected of CHB need a permanent pacemaker and around 20% may die in the perinatal period [7].

Serial foetal echocardiograms must be performed between 18th and 28th weeks of pregnancy to all women with anti-Ro and/or anti-La antibodies. If a case of incomplete heart block, myocarditis, ascites or hydrops are identified, therapy with fluorinated steroids – dexamethasone or betamethasone, which cross the placental barrier – is recommended because there is a chance for reversibility (total or partial) [7]. Recently, two clinical trials have failed to reduce the expected rate of recurrent CHB (20%) in women treated with IVIG during pregnancy [39,40]. On the other hand, a recent case–control study has suggested a protective effect of hydroxychloroquine on the development of cardiac manifestations in children with NNL born to mothers with lupus and anti-Ro/anti-La antibodies [41].

Pharmacological therapy during pregnancy

One of the critical issues in managing women with SLE during pregnancy is choosing the right medication to treat the mother without harming the baby. Unfortunately, most information regarding drug safety in pregnant women comes from case series or case reports. A recent consensus document has established, after an extensive literature review, the safety of a number of drugs commonly used in pregnant women with rheumatic diseases [22].

Nonsteroidal anti-inflammatory drugs are generally safe; however, these drugs may also cause fluid retention and worsen hypertension and renal function. They should be avoided in the last weeks of pregnancy because of the risk of premature closure of the ductus arteriosus.

With the exception of fluorinated compounds (dexamethasone and betamethasone), corticosteroids are mostly inactivated by placental hydroxylases, so the baby keeps virtually unexposed. However, they can cause important medical and obstetric problems, including diabetes, hypertension, preeclampsia and premature rupture of membranes [10,11]. We strongly recommend against the prolonged use of more than 5 mg d^{-1} of prednisone/prednisolone. In cases of severe activity, intravenous pulses of 250 or 500 mg of methylprednisolone can be used safely [8]. Most immunosuppressive drugs (cyclophosphamide, methotrexate, mycophenolate, leflunomide) are contraindicated during pregnancy. The exceptions are azathioprine, cyclosporine and tacrolimus [22].

Hydroxychloroquine constitutes the cornerstone of therapy in patients with lupus because of important beneficial effects on activity, damage, thrombosis and long-term survival [42]. The safety of hydroxychloroquine in pregnant women with lupus or other connective tissue diseases is well documented without any unexpected malformation or cases of ocular, auditory or neurological toxicity [42,43]. In addition, discontinuation of hydroxychloroquine during pregnancy can result in a flare of SLE [17]. Thus, antimalarials should not be withdrawn during or in prevision of pregnancy. At most, hydroxychloroquine

could be used instead of chloroquine, given its more favourable safety profile for the mother.

Experience with biological drugs in pregnant women is not large. However, a recent systematic review suggests the safety of anti-TNF drugs (infliximab etanercept, adalimumab), mainly in pregnant women with rheumatoid arthritis and Crohn's disease [44]. On the other hand, data regarding rituximab are more scarce, pointing however to a high incidence of lymphopenia in the offspring [44].

Low-dose aspirin and dipyridamole are safe, whilst the use of ticlopidine and clopidogrel is not recommended. Likewise, heparin in all forms does not cross the placenta and can be safely used in pregnant women. On the contrary, warfarin and coumadin must be avoided during the organogenesis (weeks 6–10) because of the well-defined warfarin embryopathy [22]. Women receiving heparin during pregnancy, as well as those treated with corticosteroids or at risk for osteoporosis, should receive calcium plus vitamin D until the end of lactation [5].

Many of the most common antihypertensive drugs are contraindicated during pregnancy (angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, diuretics). The toxicity associated to these drugs is mainly at the level of foetal kidneys, causing renal failure and oligoamnios. Embriopathy is not a major issue, however, a small increased risk for congenital malformations has been found after first trimester maternal exposure to angiotensin-converting enzyme inhibitors [45]. Thus, treatment of hypertension during pregnancy relies on old drugs such as methyldopa, nifedipine and labetalol [46]. Other antihypertensive drugs should be discontinued as soon as pregnancy is confirmed.

Lupus pregnancy management plan

Adequate pregnancy care of women with SLE rests on three pillars: a coordinated medical-obstetrical care, an agreed and well-defined management protocol and a good neonatal unit. In this setting, preconceptional counselling is essential to estimate the chance of both foetal and maternal problems and to provide the patient with reliable information regarding her specific risk for complications and the expected management plan (Table 2). A complete set of autoantibodies should be available before pregnancy, including aPL (aCL, anti-β2-glycoprotein I and LA) as well as anti-Ro and anti-La antibodies, given their close link with specific pregnancy complications. Women with active lupus should delay pregnancy until a quiescent phase of the disease, especially in the event of renal or neurological involvement. Women with a high degree of irreversible damage are more likely to suffer complications and even further damage during and after pregnancy particularly those with chronic renal, lung or heart disease. Pregnancy may be contraindicated in some situations (Table 3).

Table 2 Preconceptional visit checklist

Age?
Any previous pregnancy?
Previous pregnancy complications?
Presence of severe irreversible damage?
Recent or current lupus activity?
Presence of antiphospholipid antibodies/syndrome?
Positivity of anti-Ro/anti-La?
Current treatment: any ''forbidden'' drugs?*
Other chronic medical conditions? (Hypertension, diabetes, etc.)
Smoking?

*Including cyclophosphamide, methotrexate, mycophenolate, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics and statins.

This is also the time to evaluate the safety of the treatment received by the patient. Most forbidden medications can (and should) be stopped at this point and be substituted by alternative drugs. Smoking should be also strongly discouraged.

Women considered to be at high risk should be best managed in a combined medical-obstetrical clinic throughout the whole pregnancy. The general schedule includes more frequent visits as pregnancy progresses. Blood pressure should be measured on each visit, but women with hypertension, previous preeclampsia or past or present lupus nephritis should also provide additional home measurements. Likewise, regular urine analysis is essential to detect proteinuria, which could be the first sign of impending preeclampsia or renal lupus flare. Doppler studies of the placental vessels are very useful to estimate placental function and to predict the occurrence of complications such as preeclampsia and foetal distress. Uterine Doppler studies are recommended around the 20th week and

Table 3 Contraindications to pregnancy in women with systemic lupus erythematosus

Severe pulmonary hypertension (estimated systolic PAP > 50 mm Hg or symptomatic)
Severe restrictive lung disease (FVC < 1 L)
Heart failure
Chronic renal failure (Cr > 2·8 mg dL^{-1})
Previous severe preeclampsia or HELLP despite therapy with aspirin and heparin
Stroke within the previous 6 months
Severe lupus flare within the previous 6 months

PAP, pulmonary arterial pressure; FVC, forced vital capacity.

repeated 4 weeks later if abnormal. Umbilical Doppler ultrasound after the 24th week may show absent or even reverse diastolic flow, a sign of impending placental insufficiency and foetal distress. The finding of abnormal Doppler studies is considered an adverse prognostic sign that increases the risk of adverse outcomes. On the other hand, the negative predictive value of this test is higher as repeated normal results are associated with very low frequency of obstetric complications [47,48]. Repeated ultrasound examination of baby's heart is needed between the 18th and the 28th weeks when the mother is anti-Ro and/or anti-La positive to detect congenital heart block [7].

The postpartum period should be considered high risk for women with SLE, with several possible complications such as lupus flares, and, in women with aPL, thrombosis. A close surveillance within the first months after delivery is thus warranted.

Acknowledgements

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