

Update on systemic lupus erythematosus pregnancy

Irene Iozza¹
 Stefano Cianci¹
 Angela Di Natale²
 Giovanna Garofalo²
 Anna Maria Giacobbe²
 Elsa Giorgio²
 Maria Antonietta De Oronzo³
 Salvatore Politi¹

¹ Santo Bambino Hospital, Department of Microbiological and Gynecological Sciences, University of Catania, Italy

² Policlinico Universitario "G. Martino", Department of Obstetrics and Gynecology, University of Messina, Italy

³ Department of Gynecology, University "Campus Bio-medico", Rome, Italy

Corresponding author:

Irene Iozza: Department of Microbiological and Gynecological Sciences, Santo Bambino Hospital, University of Catania, Italy
 Call: +39-3407103884
 ireneiozza1983@libero.it

Summary

Women with Systemic Lupus Erythematosus (SLE) still face significant risks when embarking on a pregnancy. Improvements in the field of pathophysiology, in diagnosis and a greater number of therapeutic options in the treatment of SLE, have made the medical community regard these patients with less trepidation. Despite these advances, however, the risk of significant morbidity to both the mother and the fetus still exists.

The interaction of lupus and pregnancy is very complex: the consensus is that pregnancy can worsen the lupus disease process, even if this is not predictable, and pregnancy can mimic the clinical manifestations of lupus, particularly pre-eclampsia/eclampsia.

More specifically, pregnancy is associated in 50 to 60% of cases with a clinical flare manifesting as renal or hematological symptoms. Severe flares are uncommon (10%) and the risk of maternal death is now 2 to 3%. The risk of the fetus remains high, however with increased risk of spontaneous fetal wastage and premature births, by 4.8 and 6.8 times, respectively. It is well documented that antiphospholipid syndrome and antiphospholipid antibodies are strongly associated with fetal wastage. Low-dose aspirin or heparin improves fetal outcome in these cases.

Timing a pregnancy to coincide with a period of disease quiescence for at least 6 months strongly in-

creases the chances for a healthy and uneventful pregnancy for both mother and baby.

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 pre-eclampsia and foetal distress.

Women with SLE frequently need treatment throughout pregnancy based on hydroxychloroquine, low-dose steroids and azathioprine.

This update, based on previous available literature, should inform rheumatologists, obstetricians and neonatologists who guide patients in their reproductive decisions.

Key words: Fetal loss; Lupus nephritis; Antiphospholipid syndrome; Congenital heart block; Anticardiolipin antibodies; Systemic lupus erythematosus.

Introduction

SLE is a multisystem auto-immune and hormone-dependent disease, the manifestation of which requires genetic as well as certain provoking factors.

It predominantly affects women of childbearing age who, generally, have the same fertility rates as the healthy population. The disease onset peak occurs at 25–35 years of age (1,2).

Infertility in SLE is usually due to drugs, especially to cyclophosphamide-induced ovarian failure that is closely related to the total drug dose and age of 35 years or more when exposed (3).

Our understanding of the relationship between pregnancy and systemic lupus erythematosus has been evolving: pregnancy outcomes have improved dramatically over the last 40 years, with the pregnancy loss rate falling from 43% in the 1960s to 17% by 2000 (4).

Just 20 years ago, women with systemic lupus erythematosus (SLE) were advised against pregnancy due to fear of irreversible consequences for the mother. Today the scenario has changed but pregnancy should be considered a high-risk period during the course of lupus, with a large number of potential complications that can influence the course of the disease as well as the final result of pregnancy itself.

This overview highlights the current perspectives of pregnancy outcome in patients with SLE on the basis of the recent literature.

Antenatal counseling

Educating patients about appropriate contraception is key to avoiding unplanned pregnancies. Women with

rheumatologic disease should never have the impression that contraception is off-limits. The three main types of contraceptives available to all women with rheumatologic disease are barrier methods, progestin-only methods and the intrauterine device (IUD).

Controlling disease, by ensuring pregnancy is timed to disease quiescence, continuing immunosuppression and close rheumatologic follow-up are important methods to improve the odds for pregnancy success (5).

Pre-pregnancy counselling includes pertinent information about the risks of adverse outcomes, both for the baby and herself, and the planning of antenatal care. It's also essential in order to estimate the chance of both fetal and maternal problems.

The disease is not in itself a contra-indication to pregnancy, with the exception of organ-system complications such as pulmonary hypertension and renal failure. Also, the degree of lupus activity and irreversible organ damage should be determined. To minimize the risk of flare during pregnancy, it should be inactive for at least 6 months prior to conception.

The medication that the patient is taking to control her disease would also need to be reviewed at this time to evaluate their safety. Most forbidden medications should be stopped and be substituted by alternative immunosuppressant and anti-hypertensive drugs (6).

SLE flare

Clinical and immunological features of lupus activity may be different during pregnancy. Fatigue and mild arthralgia are common among normal pregnant women and can be confused with SLE flares. Likewise, edema normally appears during the last phases of pregnancy and, in the absence of hypertension and/or proteinuria, is not a warning sign. On the laboratory side, complement levels tend to rise during pregnancy, thus reducing their ability to act as useful markers of disease activity. The variation of C3 and C4 levels, rather than their absolute values, should be taken into account (7).

Lupus activity scales that are specific for pregnancy have been established but the clinical recognition of SLE flares still relies on the skill of the physician.

About 20% of flares associated with pregnancy develop within 3 months after delivery.

There is no evidence that prophylactic steroids lower the frequency of flares, and there are significant adverse effects during pregnancy: premature rupture of membranes; infections; intra-uterine growth restriction; hypertension; gestational diabetes; osteoporosis; and avascular necrosis (8).

Maternal morbidity might be potentially life threatening during an SLE exacerbation, and treatment itself is limited by pregnancy because some of the drug therapies are teratogenic and fetotoxic.

Factors predisposing to SLE flare during pregnancy

Pregnancy increases the likelihood of a lupus flare.

It is not possible to predict when, or if, an individual patient will flare and, although it is more likely if disease has been active within 6 months of conception, SLE remains stable in about 30% of the patients (9).

Overall, most flares during pregnancy occur in the second and third trimesters.

Lack of estrogen and progesterone serum level increase in SLE pregnant women during the second, and even more the third trimester of gestation, seems to be related to placental compromise.

Another significant change is the maternal augmentation of circulating blood volume and a higher glomerular filtration rate, which facilitates the onset of lupus nephritis in women with active lupus, resulting from an increased tendency for glomerular deposit of circulating immune complex. It is reported that a high level of anti-dsDNA antibodies correlates the high risk of disease exacerbation and fetal prematurity.

Disease activity and pregnancy outcome

Women with SLE had a 2- to 4-fold increased rate of pregnancy complications.

SLE tends to flare during pregnancy and the highest exacerbation rates were in the third trimester. Most flares are mild, with cutaneous and joint disease being the most common manifestations (10,11).

Moreover pregnancy outcome is influenced by the following factors: placental dysfunction, antiphospholipid antibodies (aPL), pre-conceptual lupus activity, the severity of renal involvement, and the onset of SLE during pregnancy. A previous complicated pregnancy is, by itself, an important adverse prognostic variable.

The presence of aPL is a predictor of maternal thrombosis, embryo/fetal loss and pre-eclampsia, women with aPL and recent thrombosis should advise against pregnancy (7).

Chronic renal failure is also associated with hypertensive disorders and miscarriage, the risk of which increases sharply in women with serum creatinine levels over 3 mg dl (12).

Pregnancy should be considered absolutely contraindicated in women with symptomatic pulmonary hypertension, which carries a higher than 30% maternal mortality during late pregnancy and the puerperium (13).

Medical complication and management plan of SLE pregnancy

The management of pregnancy in SLE should start before conception so as to optimize maternal health (14).

The risk of maternal death was more than 20-fold higher than the non-SLE population (0.32% among all SLE pregnancies).

The risk for sepsis (0.24 of every 100 patient years) and pulmonary infection (1.4/100 patient years) was several fold higher among women with SLE and postpartum infections occurred slightly more commonly among women with SLE (OR: 1.4, $P < 0.001$) caused by both disease-related immune dysregulation and immunosuppressive therapy (15,16).

Hematologic complications are common among lupus patients and so not surprisingly among lupus pregnancies.

Anemia was diagnosed in more than 12% of SLE pregnancies at the time of delivery. Thrombocytopenia, a common manifestation of lupus, was identified 8 times as often in SLE as in non-SLE pregnancies.

Interestingly, the rate of postpartum hemorrhage was only slightly higher than in the remainder of the population (OR: 1.2, $P < 0.001$).

The risk for venous thromboembolism was 5- to 8-fold higher and the risk of stroke was 6.5-fold higher for women with SLE compared with other women.

Preeclampsia was diagnosed in 22.5% of women with SLE against 7.6% in the general population.

The general schedule includes more frequent visits as pregnancy progresses, with weekly visits during the last 8 weeks of pregnancy.

Close monitoring of blood pressure on each visit, but women with hypertension, previous pre-eclampsia 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.

Anti-DNA and complement levels may help in monitoring SLE activity; however, the sensitivity of the latter is lower during pregnancy as increased values are normal in this period.

Doppler assessment of uterine artery blood flow at 20 and 24 weeks is useful in predicting pre-eclampsia and intra-uterine growth restriction. Assessment of umbilical flow is helpful in the presence of intra-uterine growth restriction (1).

The finding of persistently high resistance and early diastolic notch is associated with an increased risk of pre-eclampsia.

Repeated ultrasound examination of baby's heart is needed between the 18th and 28th weeks when the mother is anti-Ro and/or anti-La positive in order to detect congenital heart block (17).

During pregnancy, C3 and C4 may rise to supranormal levels, and thus a flare with complement activation may occur despite apparently normal levels of C3 and C4. However, if C3 or C4 levels drop by more than 25%, this may be reasonably ascribed to disease activity (18).

The blood tests should be done in order to monitor haemoglobin levels and platelet count because they can be affected by lupus-related immune haemolytic anaemia and thrombocytopenia caused by heparin therapy or by HELLP syndrome.

The laboratory tests should be done monthly until 20 weeks of gestation, every 2 weeks from 20 to 32 weeks, and weekly thereafter to determine the best time for inducing labor. Even with these precautions, however, preterm birth remains common.

Lupus Nephritis

Theoretically, several factors can account for the increased frequency of fetal loss in SLE patients, but in a recent multivariate analysis, maternal renal disease was the only statistically significant predictor for fetal loss, hypertension and for poor fetal outcome.

The risk of fetal loss in lupus nephritis patients at conception (serum creatinine > 1.6 mg/dl and clearance < 40 ml/min) has been established as between 12 and 38% compared to 8% in the general population.

Women with nephrotic proteinuria do have a tendency to deliver prematurely (34%) and they show intrauterine growth retardation in 30% of cases (19).

On the contrary, preeclampsia is more likely to occur in women with renal disease, arterial hypertension and aPL (20,21).

In general, women with SLE uncomplicated by hypertension or renal impairment prior to conception have successful pregnancies, and pregnancy does not have an adverse effect on the progression of renal disease (19,12,22).

Exacerbation of the disease involving kidney and central nervous system in the 6 months prior to pregnancy may cause permanent deterioration and death of the patient (23).

Women with nephrotic syndrome are at increased risk of thrombosis and therefore should be treated with low-dose aspirin throughout the pregnancy, independent of aPL status.

If proteinuria is documented on urine analysis, the urine sample should be sent for microscopy to look for fragmented red cells and red cell casts, which are predictive of active renal disease. Differentiating lupus flares from pregnancy-related physiological changes or active lupus nephritis from pre-eclampsia often poses a challenge to the physician. At times, these conditions may co-exist 'cause 2.7 - 30 % of pregnancies were complicated by preeclampsia: a rate up to 5.7-fold higher than expected.15.

Features that suggest a renal flare include a rise in ds-DNA antibodies, low or dropping complement levels, clinical evidence of a lupus flare in other organs, and active urinary sediment.

Pre-eclampsia is suggested by rising uric acid and liver enzyme levels in the presence of inactive urinary sediment. The distinction is important clinically as the treatment for preeclampsia (delivery) and lupus nephritis (immunosuppression) are different.

Renal disease flares must be managed actively and corticosteroids are the drugs of choice.

Pre-existing renal involvement in the form of lupus nephritis is clearly a risk factor for hypertensive disease during pregnancy, but it does not contraindicate gestation provided that careful planning of conception and multidisciplinary monitoring and treatment are carried out (24).

Antiphospholipid syndrome

Given that lupus is a chronic inflammatory disease with thrombophilic antibodies that can result in placental insufficiency, this abnormal maternal environment might impair fetal growth even in the predisease state.

Approximately 30 e 40 % of women with SLE have aPL antibodies. For a diagnosis of APS, the clinical features of previous vascular thrombosis or obstetric complications must be present in addition to aPL.

In pregnancy, aPL increases the risk for both maternal (thrombosis, pre-eclampsia) and fetal complications (early and late miscarriage, prematurity, intra-uterine growth restriction and oligohydramnios), pre-eclampsia, Hemolysis Elevated Liver-enzymes Low Platelets (HELLP), placental abruption and fetal death.

Pregnancy losses occur in more than 50% of women with medium or high immunoglobulin (Ig) G anticardiolipin (aCL) tests and are more likely in women with a history of at least one fetal death (25).

The aborted fetus usually appears normal. Although some babies born to mothers with APS may have posi-

tive aCL tests, complications in neonates due to these antibodies are unusual.

Anticoagulation is the preferred treatment: the current choices lie between aspirin, heparin or both (26,27).

Low-dose aspirin should be taken by all women with aPL, if possible before conception.

Optimal treatment for women with one or more late pregnancy losses (second/third trimester) but no history of thromboembolism is controversial, most obstetricians support the use of heparin in addition to low-dose aspirin (25,26).

Intravenous immunoglobulin (IVIG) has also been used during pregnancy, usually in conjunction with heparin and low-dose aspirin, especially in women with particularly poor past obstetric histories or recurrent pregnancy loss despite treatment with aspirin and heparin.

Women with APS on warfarin because of previous thrombosis, who want to become pregnant, should be switched to subcutaneous heparin early enough to ensure that there is no fetal exposure during weeks 6 and 12 of gestation. Some physicians prefer to switch before conception is attempted, whereas others do so as soon as pregnancy is determined (28,29).

Both warfarin and subcutaneous heparin are compatible with breastfeeding.

Placental pathology in SLE pregnancy

Placental weight of the systemic lupus erythematosus group was at least 1 SD less than the expected mean for gestation in more than half of placentas. Several mechanisms have been proposed. Immunoglobulin and complement deposition in the walls of decidual blood vessels cause vasoconstriction and thrombosis and it suggests that maternal autoantibodies and immune complexes are important. APL antibodies can also cause direct damage to the placental phospholipid membrane, as a consequence of which the placental growth and the foetal-maternal circulation is compromised.

Placental villi are much thinner and slimmer in appearance and scarce in number, with fewer ramifications. Placental villus dysplasia is caused by placental vasculopathy that is autoimmune in nature.

Granular IgG, IgA, IgM, and C3, as well as immunocomplex, especially DNA-anti-DNA-Ab complex deposits, can be found on the wall of villus vessels or in trophoblast membranes by immunohistology. Excessive intervillous fibrin deposition and infarction were noted in almost all cases. Low placental weight appears directly related to restricted fetal growth but was not significantly related to fetal death (30,31).

In some instances, however, the extent of placental damage does not appear to be sufficient to account for the degree of fetal distress.

Pharmacological therapy during pregnancy

Drugs that are considered to be safe in pregnancy are: prednisolone; azathioprine; cyclosporin A; and hydroxychloroquine.

Corticosteroids have been used extensively and safely in patients with SLE during pregnancy.

With the exception of fluorinated compounds (dexam-

ethasone and betamethasone), corticosteroids are mostly inactivated by placental hydroxylases. In the case of maternal administration of prednisone or prednisolone, the fetal blood level is nearly 10% of the maternal level. On the other hand, the fetal liver is not so capable of converting prednisone to its active metabolites. Therefore a low to moderate dose of maternal prednisone administration will not have much influence on the fetus. A low dose of prednisone may have a prophylactic role in preventing maternal SLE flaring up without many side-effects in the fetus. Despite this lack of direct effect on the baby, they can, especially in high doses (>20 mg/day), cause important medical and obstetric problems, including diabetes, hypertension, pre-eclampsia and premature rupture of membranes (32).

In cases of severe activity, intravenous pulses of 250 or 500 mg of methylprednisolone can be used safely (33). Antimalarials are extensively used in the management of SLE, being a good steroid-sparing drug. They have several types of pharmacological effect, such as immune modulation including protection against flares, antiplatelet aggregation, and lowering cholesterol level. Some studies have documented fetal safety in maternal antimalarial therapy during pregnancy, and a survey in 2002 showed that the majority of lupus experts tended to continue this drug during pregnancy (34,35).

Nevertheless the drug can cross the placenta and avidly bind to pigmented tissue, especially the fetal retina.

Hydroxychloroquine should not be stopped in early pregnancy, because this could precipitate a flare, and its long half-life means the fetus would continue to be exposed to the drug for several weeks, even after discontinuation. As a more cautious strategy, SLE patients should have a stable disease condition, without antimalarials, when preparing for a possible pregnancy (36,37,38).

Specific therapy for lupus flares depends on severity and organ involvement.

Rash and arthritis can be managed with Nonsteroidal anti-inflammatory drugs (NSAIDs), low-dose prednisolone (up to 10 mg/day) or hydroxychloroquine.

Serositis usually responds to low-dose prednisolone.

Renal or neuropsychiatric involvement and other severe manifestations such as cutaneous vasculitis need more aggressive treatment. In these cases, higher doses of prednisolone are used. In order to achieve the goal of rapid tapering of prednisolone without leaving SLE untreated, the early use of azathioprine is advocated. This is usually well tolerated and has been used in many pregnant women with auto-immune diseases.

Ibuprofen and diclofenac are generally safe during pregnancy but should be avoided after 34 weeks of gestation (due to risk of premature closure of the ductus arteriosus).

Paracetamol and codeine-based analgesia may be used and are preferable for pain relief.

Antihypertensive drugs are frequently needed in pregnant women with SLE but many of the most common drugs in this group are contraindicated during pregnancy (angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, diuretics), given their toxicity on the fetal kidneys, causing renal failure and oligoamnios. Thus, treatment of hypertension before conception or during pregnancy relies on old drugs such as methyldopa, nifedipine and labetalol.

Among antiaggregant drugs, 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. However, exact dosages and durations of aspirin and heparin that optimize fetal outcome have yet to be established.

Warfarin and coumadin must be avoided during the organogenesis.

Methotrexate, mycophenolate mofetil and cyclophosphamide are contra-indicated during pregnancy.

The biological drugs (e.g. anti-tumor necrosis factor (TNF) agents and rituximab) are currently not recommended during pregnancy, due to the potential transplacental transfer (39).

Puerperium

A close surveillance in the first 4 weeks after delivery is warranted, especially in women with recent activity or previous severe disease. However, no specific prophylactic therapy (such as increasing the dose of steroids) is recommended.

The puerperium is also a high-risk period for thromboembolic complications. This is especially true in women with aPL, in whom adequate thrombo-prophylaxis with low molecular weight heparin should be extended for 4 to 6 weeks after delivery. Those with a previous history of thrombosis can be back on their usual full anticoagulant therapy within 2 to 3 days post-partum. Breastfeeding is possible if the mother is taking glucocorticoids or antimalarials (e.g. hydroxychloroquine) but not if she is on immunosuppressive agents. Aspirin levels in breast milk peak 2 h after the serum peak; thus, low-dose aspirin therapy does not contraindicate breastfeeding at a distance from dosing.

It should be remembered that both, warfarin and heparin, are perfectly safe during lactation.

Neonatal SLE and anti-Ro/SSA antibodies

The newborn may be affected by the onset of neonatal lupus erythematosus (neonatal LE), manifested as a skin rash, congenital heart block (atrial-ventricular), and an abnormal low blood count, such as leucocytopenia, anemia, and thrombocytopenia.

Neonatal LE is caused by the passage through the placenta of anti-Ro/SSA and anti-La/SSB antibodies that may exert direct toxic effects on the cardiac conduction tissue, impairing the normal function of the sinus and the atrio-ventricular node by interfering with the calcium channels.

Neonatal lupus with or without congenital heart block is exceedingly rare, being seen in the 1% of SLE women who have anti-SSA (Ro) and/or SSB (La) antibodies (40,41,42).

Neonatal lupus rash manifests as annular inflammatory lesions similar to those of adult subacute cutaneous SLE, usually on the face and scalp, which appear after sun or ultraviolet light exposure in the first 2 weeks of life. The rash disappears spontaneously within 6 months as do blood count abnormalities.

In severe cases, topical steroids may be used. Residual

hypopigmentation or telangiectasia may persist for up to 2 years, but scarring is unusual (43).

Neonatal SLE, although rare, carries a significant mortality rate (24% of cases) and morbidity when the fetal heart is the targeted organ and almost half of the surviving children require pacing in the first year of life.

It may occur in the offspring of women with these antibodies, regardless of their clinical diagnosis and even if the mother is asymptomatic, with a recurrence rate of 16% in subsequent pregnancies (44).

Congenital heart block occurs between 18 and 30 weeks, and fetal echocardiography should be performed over this period to enable early detection.

Incomplete blocks may resolve upon treatment of the mother with high-dose betamethasone (12 mg/week). Although complete heart block is not amenable to curative treatment, its adverse effects on heart function can be corrected by betamethasone therapy (45).

Due to a recurrence rate of 16% in subsequent pregnancies, prophylaxis therapies, including treatment with intravenous immunoglobulin between 12 and 24 weeks of gestation has been suggested in women with previously affected in congenital heart block children (46,44,47). Neonatal lupus is not closely related to adult lupus. The affected infant will not usually develop lupus while growing up.

When hydrops fetalis develops, dexamethasone, salbutamol or digoxin may all have a place; however, as always, fetal benefit must be weighed against maternal risk.

Other rarer features of neonatal SLE are abnormal liver function tests and thrombocytopenia; these manifestations are transient, resolving by the age of 1 year, and infants are usually asymptomatic.

Conclusions

The majority of women with SLE can have a successful pregnancy. However, pregnancy constitutes a major challenge for women with systemic lupus erythematosus when compared with other women, resulting in more cesarean births (48% vs. 21%), maternal death, preeclampsia, preterm labor (36% vs. 18%), thrombosis, infection, and hematologic complications during pregnancy. Severe kidney, lung or heart disease are life-threatening complications of SLE and patients should be discouraged from getting pregnant, due to the high risk of both maternal and fetal complications in terms of spontaneous abortion (10–35% of cases), prematurity, fetal growth retardation (10–66%) and high rate of perinatal mortality (48).

These elevated risks make clear the need for close monitoring by coordinated obstetric care and rheumatologists during pregnancy to maximize the chance of success.

Inactive lupus nephritis and normal renal functions at conception appear to be the only predictors of a favourable maternal outcome of pregnancy so it is essential that the maternal disease is well controlled prior to, during and after pregnancy to ensure the best possible outcome for the mother and child.

In conclusion, data from literature confirm a greater frequency of hypertensive complications and stillbirths in lupus-related pregnancies and the adverse effect of lu-

pus on fetal outcomes. The new and most important finding is that the fetus does not thrive as well in the abnormal immune/vascular environment of mothers who are destined to have lupus. This suggests that, as in diabetes mellitus, there is a predisease state in lupus that adversely affects fetal outcomes (49).

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