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Lupus Pregnancy: Risk Factors and Management

Jose Ordi-Ros, Cristina Sole Marce
and Josefina Cortes-Hernandez

Abstract

Systemic lupus erythematosus (SLE) mainly affects women in the fertile age of life. A patient with SLE is as fertile as the general population except for treatment with drugs with ovarian toxicity, severe flare of the disease, or autoimmune oophoritis for anti-ovarian antibodies. Pregnancy in a woman with SLE implies greater maternal and fetal mortality and morbidity. Fetal loss, premature birth, intrauterine growth restriction associated with antiphospholipid antibodies (aPL), and neonatal lupus associated with anti-Ro are important fetal problems. Similarly, preeclampsia and lupus nephritis may lead to diagnostic confusion. Treatment options during pregnancy are limited to a few safe medications, which further restricts options. The loss of refractory pregnancy associated with antiphospholipid antibodies and the complete heart block associated with anti-Ro antibodies remain unresolved problems. The planning of pregnancy with sustainable treatments during pregnancy, no flare of SLE in the previous 6 months, and absence of nephritis are important for a good maternal and fetal prognosis. A gestation planning, multidisciplinary approach, and close monitoring are essential to obtain optimal results.

Keywords: Lupus, pregnancy, fertility, antibody, treatment

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women of fertile age. Pregnancy causes concern for the majority of patients with SLE. The risk of the disease flare during pregnancy, the possibility of fetal loss, and the safety of drugs during pregnancy are of concern. A better understanding of the pathogenesis of SLE and good use of immunosuppressive drugs allows us to better control the disease, and we should not deprive patients with SLE of the opportunity to have children. Prepregnancy information and collaboration between specialists, such as obstetricians and perinatologists, are essential to optimize maternal and fetal outcomes in SLE pregnancies. In this chapter, important issues related to fertility, optimal time of conception, risk of disease flare during pregnancy, course of pregnancy, fetal outcome, safety of various medications used to control SLE during pregnancy and lactation, and a contraceptive education are discussed [1].

2. Systemic lupus erythematosus fertility

Fertility in patients with SLE is not greatly affected by the diagnosis of the disease. The decrease in fertility in SLE can be a consequence of the drugs used in the treatment of these patients, the flare of the disease, the organic damage caused by the disease, or advanced age. The use of cyclophosphamide (CYC) induces the majority of nonage-related infertility in patients with SLE, although the increasing use of mycophenolate mofetil (MMF) for the treatment of renal and extrarenal manifestations reduces the incidence due to its null ovarian toxicity. The risk of infertility due to CYC is associated with both the cumulative dose and an older age (>37 years old) of the woman at the time of treatment. The probability of maintaining fertility after treatment is greater for patients under 30 years of age, six or less monthly intravenous pulses, a cumulative dose of less than 7 g, and lack of amenorrhea before or during drug administration. It is less likely that other treatments in SLE have a significant impact on fertility, although nonsteroidal anti-inflammatory drugs (NSAIDs) have been suggested as possible contributors to infertility and it is suggested that high doses of corticosteroids have some effect on the cycle menstrual through its effect on the hypothalamic pituitary axis (HPA).

Patients with SLE may have menstrual disturbances or even amenorrhea secondary to very active disease. In addition, serum levels of anti-mulleriana hormone (AMH) are lower in patients with SLE not treated with CYC than in controls matched by age. It is important to emphasize that renal failure induced by lupus glomerulonephritis can cause hypofertility or infertility due to an alteration of the HPA, which can be reversed with kidney transplantation.

The profile of autoantibodies does not seem to affect fertility in women with SLE. However, the study of aPL in women with lupus is essential for predicting gestational risk, although recent controlled studies do not support an association between aPL and infertility or in vitro deficient fertilization (IVF). Evaluation or treatment of aPL in infertile women is not recommended.

Older age is an important factor of infertility in SLE, as it is in the general population. Female fertility decreases with age due to the progressive loss of the ovarian reserve; many patients with SLE are older when they try to conceive and may encounter difficulties related to age. The onset of SLE is more frequent in the first years of reproduction, and it is advised to avoid pregnancy when the disease is active. Premature ovarian failure (persistent amenorrhea with elevated levels of follicle-stimulating hormone before age 40) may be of autoimmune etiology in the general population but is rarely associated with systemic autoimmune diseases such as SLE [1, 2]. The study of anti-ovarian antibodies has contributed little to this pathology. However, treatment with corticosteroids and/or immunosuppressants has reversed the process in some cases.

2.1 SLE fertility preservation

Preserving fertility in women with SLE involves limiting cytotoxic drugs when possible and protecting the ovaries during treatment; however, prompt and effective therapy for a severe disease often takes precedence. The cryopreservation of oocytes or embryos is an effective option but requires ovarian stimulation, which may be impractical given the usual need to institute therapy quickly to avoid damage, as well as the risk of hyperstimulation in a patient with active SLE. The age of the patient to whom CYC is administered is not modifiable, but an effort must be made to minimize the total dose of CYC. The use of MMF may be the best option. Treatment with agonists of the gonadotrophic hormone receptor (GnRH) during

CYC therapy to minimize ovarian toxicity has become a common practice. Ovarian toxicity amenorrhea due to CYC has been the classic clinical sign. Now, the measurement of the AMH provides us with a better evaluation of the ovarian reserve. In a study of patients with SLE who received leuprolide with a GnRH agonist between 10 and 14 days before the CYC pulse therapy, a 68% increase in the ovarian reserve was estimated compared to patients with SLE who had not received this treatment. The GnRH agonist should not be administered immediately before the CYC. When administered during the follicular phase of the cycle, it can stimulate the ovaries and worsen ovarian damage. Patients without therapy with GnRH agonists before their first infusion can start treatment after the first cycle and receive treatment at monthly intervals thereafter [2].

3. Contraception control

SLE patients may be strongly advised to avoid pregnancy, particularly when they have severe disease-related damage or active disease or are taking teratogenic medications. Consequently, contraceptive options should be discussed with all female patients of reproductive age. Counseling patients to defer pregnancy relies on the assumption that they will utilize safe and effective contraception. In practice, SLE patients currently underutilize effective contraception, even those taking teratogenic medications [2]. Contraceptives vary in safety and efficacy. Long-acting reversible contraceptives such as intrauterine devices (IUDs) or subdermal implants have the greatest efficacy. IUDs generally contain either progesterone (levonorgesterol) or copper. Although IUDs have a low risk of infection, patients treated with immunosuppressive medications have not been specifically studied. However, HIV-infected women who have been studied do not have a greater risk of infection. Combined hormonal contraceptives include the pill, transdermal patch, and vaginal ring. Serious side effects include a three- to fivefold increased risk of venous thromboembolism and a twofold increased stroke risk. Medications commonly used for patients with SLE, such as warfarin and MMF, may interact with these agents and alter their efficacy. Concern regarding estrogen-induced flare previously has limited the use of oral contraceptives in patients with SLE. Two recent prospective studies in women with stable SLE showed no increased risk of flare with combined oral contraceptives. But oral contraceptives containing the progestin drospirenone can increase serum potassium and be dangerous in patients with nephritis or who also take angiotensin-converting enzyme (ACE) inhibitors. The vaginal ring and the patch may further increase thrombosis risk compared to oral combined contraceptives, and their safety in SLE has not been studied. No forms of estrogen-containing contraceptives are advised for use in aPL-positive patients due to the increased risk for thrombosis [3]. Progesterone-only contraceptives include oral and intramuscular forms, IUDs, and a subdermal etonogestrel implant. Depot medroxyprogesterone acetate (DMPA) injections may decrease bone density when used chronically, a concern in corticosteroid-treated patients. Progesterone-only contraceptives represent a safe and effective option for aPL-positive patients; with the possible exception of DMPA, the risk for thromboembolism is very low, and they may decrease menstrual blood loss. Emergency contraception can be considered for all SLE patients, including aPL-positive patients. Long-acting reversible contraceptives are preferable for most SLE patients, but every decision regarding contraception must balance the risk and efficacy of the method with the risk of unplanned pregnancy.

4. Fertility and assisted reproductive techniques

Fertility is generally unimpaired in patients with systemic lupus erythematosus (SLE), unless they have been treated with cyclophosphamide (CYC). Although CYC is less commonly used for nephritis than in the past because of the availability of MMF, prevention of CYC-induced infertility remains an important concern. Concurrent gonadotropin-releasing hormone (GnRH) analogue therapy, usually leuprolide, appears to decrease risk of premature ovarian failure by CYC. Embryo and oocyte cryopreservation is options to preserve fertility in patients who are stable enough to safely undergo ovarian hyperstimulation. Patients with lupus may undergo assisted reproduction techniques, including in vitro fertilization (IVF). Ovarian hyperstimulation syndrome (OHSS) is a rare complication of IVF resulting in a capillary leak syndrome; severe OHSS increases risk for thrombosis and renal compromise. Even in a well-controlled cycle, elevated estrogen levels may increase risk of flare and thrombosis in SLE patients. However, thrombosis in aPL-positive patients undergoing IVF is rare, but most reported patients have been treated prophylactically with anticoagulants. Prophylactic anticoagulation may be considered in patients with high-risk aPL profiles and is mandatory for those with confirmed APS. However, aPL antibodies as a cause of failed IVF or infertility is not accepted, and anticoagulation is not indicated to improve IVF cycle outcome [2, 3].

5. Preconception orientation

Good information to the patients and pregnancy planning is essential for a woman with SLE who wants a child. Pregnancy planning is a key point for women

Preconception visit checklist	Contraindications to pregnancy
Age	Severe lupus flares within the previous 6 months
Any previous pregnancy?	Severe restrictive lung disease (FVC < 1 L)
Previous pregnancy complications?	Heart failure
Presence of severe irreversible damage?	Chronic renal failure (Cr < 30 mg/dL)
Recent or current lupus activity?	Stroke within the previous 6 months
Presence of antiphospholipid antibodies/syndrome?	Previous severe preeclampsia of HELLP syndrome despite therapy with aspirin and heparin
Other chronic medical conditions?	Severe lung hypertension
(Hypertension, diabetes, etc.)	(Estimated systolic PAP > 50 mm Hg or symptomatic)
Previous nephritis or active nephritis	
Current treatment: any forbidden drugs (including cyclophosphamide, methotrexate, mycophenolate, thalidomide, or thalidomide lyks, angiotensin-converting, enzyme inhibitors, angiotensin II receptor blockers, diuretics, and statins)	
Positive anti-Ro and anti-La	
Anti-DNA, complement levels C3 and C4	
Abbreviations: PAP, pulmonary arterial pressure; FVC, forced vital capacity.	

Table 1.
Preconception visit checklist and contraindications to pregnancy in women with SLE.

with SLE. Postponing conception until the disease is inactive for at least the previous 6 months significantly improves the results. Women with irreversible lesions in vital organs are more likely to suffer maternal-fetal morbidity and mortality during and after pregnancy. The pregnancy should be delayed, such as a severe disease flare in the previous 6 months, a recent stroke, and active lupus nephritis. In some situations, pregnancy may be contraindicated (**Table 1**). A profile of autoantibodies, such as aPL (anticardiolipin, anti-β2 glycoprotein I, and lupus anticoagulant), serum levels of complement, anti-SSA, and anti-SSB antibodies [4], is essential as risk factors for complications during pregnancy. Keeping the SLE inactive and the function of organs with safe medications during pregnancy should be a goal. There is an increased risk of complications among women with severe impairment of organ function, with or without serious pre-existing damage. The care of pregnant women with SLE must focus on three mainstays: a coordinated medical-obstetrical care, a well-defined management protocol, and a well-structured prenatal follow-up.

6. Laboratory evaluation during prenatal care

In pregnancy, it is necessary to perform routine pregnancy testing plus other tests that include a complete blood count, kidney and liver function, and proteins in a 24-hour urine collection (**Table 2**). Complementary studies should include additional tests such as complement study (C3 and C4), aCL, LA, aβ2GPI, anti-DNA, anti-SSA, and anti-SSB antibodies [4]. Evaluate the activity of the disease during the prenatal phase. The hormonal changes during pregnancy cause an alteration of the domain of Th1 to Th2 lymphocytes, and, consequently, it is expected that autoimmune disorders involving the Th2 response, such as SLE, are activated. In general, it is accepted that pregnancy can lead to higher rates of outbreaks of the disease, ranging from 25 to 65%. Skin rashes and musculoskeletal symptoms are less common, while renal and hematological flares are more frequent. The risk of flare seems to be related to the onset of disease activity 6–12 months before conception. There is an increased risk of flares during pregnancy when there is lupus nephritis at conception and even in women with pre-existing nephritis in remission. One study showed an exacerbation rate of 30% of SLE activity during pregnancy or postpartum in women with pre-existing lupus nephritis. It is sometimes difficult to distinguish signs and symptoms related to pregnancy from those due to SLE. Some ambiguous manifestations such as fatigue, headaches, arthralgias, edema, hair loss, palmar and malar erythema, anemia, and thrombocytopenia can be confused with clinical manifestations of SLE. An evaluation by physicians experienced in pregnant women with SLE is important. Blood tests with basal blood counts and urinalysis with measurement of proteinuria are useful to control the state of the disease and identify the flare. The production of C3 and C4 increases in the liver during pregnancy, and, therefore, their levels may be within the range of normality in cases of active SLE. Relative variations of complement are more important than absolute levels, and a 25% drop in serum complement levels may suggest a flare of lupus. The determination of the products of complement degradation would be the best way to identify a greater activation. Currently, we have indices to measure the activity of SLE during pregnancy, such as the pregnancy activity index of systemic lupus erythematosus (SLEPDAI) and the index of lupus activity in pregnancy (LAI-P). In practice, the clinical judgment of an experienced clinician is still considered the gold standard, and these indices are essential for publications on SLE and pregnancy. The SLEPDAI scale is an instrument similar to the SLE disease activity index (SLEDAI) to evaluate the activity of lupus, assigning different scores for the

Prepregnancy	Every 6–8 weeks[1]
Complete blood count with platelets	Complete blood count with platelets
Comprehensive metabolic panel	Comprehensive metabolic panel
Prothrombin time/partial thromboplastin tine	Urinalysis with microscopy
Urinalysis with microscopy	Spot protein/creatinine ratio
24-hour urine protein and creatinine clearance[2]	Anti-dsDNA
Spot protein/creatinine ratio	Complement levels (C3, C4)
Anti-dsDNA	Uric acid
Anti-Ro/SSA and anti-La/SSB antibodies	sFlt-1/PlGF ratio (>20 weeks)
Lupus anticoagulant[3]	
Anticardiolipin IgG, IgM[3]	
Anti-β2 glycoprotein I IgG, IgM[3]	
Complement levels (C3, C4)	
Uric acid	

[1]*Adjust interval of monitoring based on clinical situation.*

[2]*In patients with proteinuria, consider repeating 24-hour urine test each trimester.*
[3]*If positive for first time, repeat in 12 weeks.*

Table 2.
Systemic lupus erythematosus pregnancy evaluation and monitoring.

various clinical and laboratory manifestations of lupus activity, however, taking into account the changes, physiological factors of pregnancy, and main pathologies of the pregnancy-puerperal cycle that can simulate an active SLE. The risk of hypertensive disorders during pregnancy increases in the context of active lupus nephritis. The frequency of preeclampsia varies from 7.5 to 22.5% for all women with SLE. Renal involvement of lupus is often associated with hypertension, and the diagnosis of preeclampsia is difficult because it may coincide with chronic hypertension exacerbated during pregnancy. Likewise, in the case of women with SLE with residual glomerular lesions, an increase in proteinuria can be observed, due to the increase in the glomerular filtration rate during pregnancy, and this fact is not related to preeclampsia. The diagnosis of preeclampsia may be more difficult due to the increase in blood pressure and previous proteinuria. The differential diagnosis of preeclampsia in patients with lupus may be facilitated by changes in the C3, C4, and CH50 measurements, since a reduction in these levels is expected during lupus activity. Other laboratory tests are useful to perform a differential diagnosis, such as an abnormal urinary sediment, erythrocytic dysmorphia or cell casts, and increased titers of anti-DNA antibodies (common in lupus nephritis). SLE of onset during pregnancy should be considered as an active lupus and may be associated with a worse outcome of pregnancy. Differentiating preeclampsia into an early SLE during pregnancy is a challenge and often delays the diagnosis of SLE. Among patients with stable SLE at the time of conception, it is expected that the activity of the disease does not worsen, and even if so, the flare is usually mild and involves some type of treatment modification.

7. Evaluation of fetal growth and vitality

Fetal complications are frequent in patients with SLE. Miscarriages and intrauterine fetal death can occur in 20% of pregnancies in patients with SLE. Patients

with a history of nephritis have a higher risk of such adverse outcomes. The rate of restriction of fetal growth (FGR) is close to 30%, even in mild disease, with an increased risk if there is renal involvement. Several studies concluded that the result of the mortality rate for women with SLE tends to be higher, a condition strongly associated with the presence of flares of the disease during pregnancy. Serial obstetric ultrasound is the most important method to guide the monitoring of fetal growth. The measurement of the length of the cranial crown in the first trimester is presented as the most accurate measurement. At 16–22 weeks of gestation, an anatomical survey should be followed that considers the diagnosis of fetal anomalies, which also allows the first growth monitoring. In each 4-week period, new scans must be performed, measuring the volume of amniotic fluid. If preeclampsia is diagnosed, the interval should be reduced. The monitoring of fetal vitality is an important part of the prenatal care of patients with SLE. This should include the nonstress test (NST), the biophysical profile (BPP), and the Doppler velocimetry of the fetal umbilical artery, beginning at 26–28 weeks and continuing weekly until birth. In patients with SLE, alterations of the umbilical artery Doppler velocimetry should be handled in a similar way to those without the condition. The normal evaluation of these tests has a high negative predictive value for fetal death. A relationship exists between abnormal uterine artery Doppler and posterior fetal loss, preeclampsia, FGR, and preterm birth. For women with anti-SSA/anti-SSB antibodies, fetal echocardiography should be performed between 18 and 26 weeks to exclude congenital heart blockage of the fetus. An urgent referral to a tertiary care center should be requested in case of abnormal fetal heart rate, mainly a low heart rate.

8. Recommended SLE treatment during pregnancy

An active SLE is harmful to the mother and the fetus, and an appropriate reflection is necessary between the risks and benefits of the indicated treatment. In practice, it is common for women with SLE to interrupt their medication before conception, for fear of fetotoxicity, which happens through medical advice and proper planning [5]. Stopping the medication can lead to an active SLE and unfavorable pregnancy outcomes. Immunosuppressive treatment in pregnant women with quiescent lupus should not be changed unless it induces fetal malformations. The glucocorticoids and antimalarials are the drugs most used in the treatment of lupus and should be maintained at the same doses during pregnancy. Prednisone at a dose of 5–10 mg/day is considered safe and sustainable during pregnancy. The mild flare of the disease can be treated with low doses of prednisone (less than 20 mg/day), and higher doses of corticosteroids, such as intravenous pulses, will be indicated to treat moderate to severe lupus activity. The antimalarial is not teratogenic and is recommended to prevent the activity of the disease and reduce the risk of cardiac neonatal lupus in patients with anti-Ro antibodies. The use of immunosuppressants is possible during pregnancy, and azathioprine is the safest. Changing other immunosuppressants to azathioprine in a patient with SLE who wants pregnancy is recommended. Some recent report describes leukopenia, thrombocytopenia, and slow development of children exposed to azathioprine during pregnancy. Cyclosporine and tacrolimus, classified as category C by the Federal Drug Association (FDA), are safe during pregnancy initially demonstrated in pregnant women with kidney transplantation. CYC should not be prescribed during the first trimester for causing fetal chromosome, if it can be used during the second or third trimester for severe flares not controlled with pulses of methyl-prednisolone or other immunosuppressants. The use of CYC during the second and

third trimesters does not seem to increase the risk of congenital anomalies, although spontaneous abortions and premature labor may be more frequent. Treatment with mycophenolate mofetil may be another option during the second and third trimesters, although more experience is lacking. Leflunomide is associated with teratogenic and fetotoxic effects in animals, and its metabolite is detectable in plasma up to 2 years after the interruption. In pregnant women, it is formally contraindicated, and pregnancy should be excluded before starting a treatment with leflunomide. Methotrexate, classified as drug X by the FDA, is teratogenic and produces abortion at high doses; therefore, it is contraindicated in pregnancy. If used in the first trimester, it is associated with FGR and some important malformations, such as absence or hypoplasia of the frontal bones, craniosynostosis, large fontanelle, and ocular hypertelorism. Thalidomide or thalidomide-like is used for the treatment of cutaneous lupus, producing malformations in the fetus, such as phocomelia by thalidomide. Rituximab has a very low transplacental transfer during the first trimester of pregnancy, and some studies of safe pregnancies and deliveries have already been reported in cases of exposure; in the second or third trimester, it can cross the placenta and induce severe neonatal lymphopenia. Therefore, in these cases, live vaccines should be avoided in these children during the first 6 months of life. High blood pressure is a common condition among patients with lupus nephritis; an adequate treatment of blood pressure during pregnancy can reduce the progression of the disease and avoid several adverse pregnancy outcomes. The labetalol, nifedipine, hydralazine, and methyldopa are safe medications to treat hypertension in pregnant women. Angiotensin-converting enzyme (ACE) inhibitors should be avoided due to their association with multiple congenital anomalies. A low dose of aspirin is recommended, since it reduces the risk of preeclampsia and perinatal death; In addition, it is associated with an increase in birth weight in those cases with risk factors, including kidney disease. Complete anticoagulation with low molecular weight heparin (LMWH) is recommended if there has been a previous thrombotic event. Calcium supplements are required, mainly for those women who use corticosteroids and heparin. Also, vitamin D supplements can be given, but it does not reduce unfavorable obstetric risks.

9. Lupus flare management during pregnancy

Many physiological changes in pregnancy can overlap with the characteristics of active disease, which makes differentiation difficult (**Table 3**). Some common laboratory tests also become less reliable: mild anemia and thrombocytopenia are common, the erythrocyte sedimentation rate (ESR) increases, and up to 300 mg/day proteinuria can occur during normal pregnancy. Complement levels increase by 10–50% during normal pregnancy and may appear to remain in the "normal" range, despite the activity of the disease. Anti-DNA antibodies may be useful in the evaluation of disease activity. The scales of activity of the specific disease of pregnancy, the activity index of pregnancy SLE (SLEPDAI), the LAI-P, and the BILAG2004-Pregnancy index have been developed with modifications in the descriptors. A combination of laboratory parameters along with clinical judgment may be the best tool to evaluate the activity of the disease. Based on the numerous risks associated with pregnancy, it is recommended that women with SLE have a preconception assessment and multidisciplinary management with maternal-fetal drugs and rheumatology during pregnancy. Active SLE at the time of conception is a predictor of adverse outcomes. It is suggested that the disease remain inactive for 6 months before attempting pregnancy. Laboratory tests should include, at a minimum, antiphospholipid antibodies (LA, IgG and IgM aCL, IgG, and

		Pregnancy changes	**SLE activity**
Clinical features		Facial flush	Photosensitive rash
		Palmar erythema	Oral or nasal ulcers
		Arthralgias	Inflammatory arthritis
		Fatigue	Fatigue, lethargy
		Mild edema	Moderate to severe edema
		Mild resting dyspnea	Pleuritis, pericarditis
Laboratory features		Mild anemia	Immune hemolytic anemia
		Mild thrombocytopenia	Thrombocytopenia
			Leukopenia, lymphopenia
		Mild increased ESR	Increased inflammatory marker levels
		Physiologic proteinuria	Proteinuria > 300 mg/day
			Active urinary sediment

Abbreviation: ESR, erythrocyte sedimentation rate.

Table 3.
Overlapping features of pregnancy and systemic lupus erythematosus (SLE).

IgM anti-aβ2GPI I antibodies), anti-Ro/SSA and anti-La/SSB antibodies, and an evaluation of renal function (creatinine, protein/creatinine ratio in urine). Women who have anti-Ro/SSA and anti-La/SSB antibodies should have intensive fetal monitoring for cardiac arrest with fetal echocardiography by weekly pulsed Doppler (to measure the mechanical PR interval) beginning at 16–18 weeks and continuing up to 26–28 weeks of pregnancy. Ideally, all women with SLE should receive HCQ and low doses of aspirin during pregnancy, unless contraindicated. Women who continue HCQ during pregnancy have fewer outbreaks of disease and better outcomes as well as mothers with positive anti-Ro/SSA and anti-LA/SSB antibodies. Low-dose aspirin initiated at 12–16 weeks of gestation reduces the risk of preeclampsia and fetal growth restriction [6]. The interruption of medications used to control the activity of the disease increases the risk of flares and complications associated with pregnancy. Serial ultrasound exams should be performed to assess fetal growth and fetal monitoring before delivery should begin in the third trimester. Renal involvement is common in patients with SLE and may be suspected in the presence of proteinuria or elevated serum creatinine. Hypertension and nephrotic syndrome consist of intense proteinuria, hypoalbuminemia, and peripheral edema, and patients have characteristically low levels of complement (C3) and high levels of anti-DNA. The involvement of the renal vasculature in cases of lupus nephritis is a sign of poor prognosis. In thrombotic microangiopathy, damage to the endothelial cells of small arterioles and capillaries results in thrombosis and mortality. Neuropsychiatric symptoms observed should be considered and excluded, including electrolyte abnormalities, infection, renal failure, and the effects of drugs. In the absence of a standard gold diagnostic test, this can represent a significant clinical challenge, especially in pregnancy and the postpartum period, where specific conditions of pregnancy, such as preeclampsia and eclampsia, can produce the same symptoms. The APS is an autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity in the presence of persistent antiphospholipid antibodies. A small subset of patients with APS (<1%) develops multiple organ failure secondary to a disseminated thrombotic disease, a condition called catastrophic APS (CAPS) that has a mortality rate of up to 50%.

The treatment of flares during pregnancy is guided by the severity and involvement of the organ, similar to the state of nonpregnancy. However, the choice of agents is limited to safe medications, as discussed above. The steroids should be used in the lowest possible doses, but short cycles of high doses can be used for flare control. NSAIDs can produce malformations, and in general their indication in the SLE is in disuse. The antimalarial should be continued throughout pregnancy. Azathioprine and anti-calcineurin can occur throughout pregnancy. Azathioprine is a safe immunosuppressant with much experience in pregnancy, although delays in the development of the offspring have recently been reported. IVIg and plasmapheresis are still alternative options, but the increased risk of thrombosis with IVIg and fluid overload should be considered, although it is rarely necessary if we exclude intravenous Ig treatment of severe thrombocytopenia in pregnancy. Physiological changes in pregnancy such as an increase in glomerular filtration rate and renal plasma flow can worsen pre-existing kidney disease. However, in theory, a rapid decrease in the levels of the pregnancy hormone, particularly estrogen, may be advantageous. It is known that the immunosuppressive drugs used to treat SLE, such as CYC, cross the placenta and have teratogenic effects. In addition, this particular medication has been associated with premature and irreversible ovarian failure.

10. Lupus pregnancy, nephritis, and eclampsia

Lupus nephritis is an important risk factor for both maternal and fetal complications. A meta-analysis of 37 studies from 1980 to 2009 included 2751 pregnancies with SLE: the SLE flare rate was 25.6%, and the rates of preterm birth and IUGR were 39.4 and 12.7%, respectively. Positive associations were identified between preterm birth and active nephritis, hypertension and active nephritis, and pre-eclampsia and history of nephritis [7]. Up to 25% of women with SLE will develop preeclampsia compared to 5% in the general population. Doctors who treat lupus and pregnancy should ask themselves questions like does the presence of increased proteinuria and hypertension represent a flare or does the presence of increased proteinuria and hypertension represent the onset of preeclampsia? At the beginning of pregnancy, the presence of new or worsening proteinuria and hypertension will almost always represent a flare of lupus nephritis. However, beyond 20 weeks of gestation, differentiating a flare of preeclampsia poses a diagnostic as well as a therapeutic challenge (**Table 4**). Flare of lupus nephritis in pregnancy may be the first presentation of lupus and is relatively rare in those without previous nephritis or inactive nephritis at the beginning of pregnancy. However, if a woman has proteinuria, hypertension, renal function decreased at the beginning of pregnancy, and a history of lupus nephritis, she is likely to have a flare of lupus nephritis. The clinical history plus appropriate biochemical investigations is key to the diagnosis of clinical complications in SLE and pregnancy. The complement should be normal or high in pregnancy because it behaves as an acute phase reactant since this is pregnancy. The decrease in complement, even within the normal range, should alert us to a possible flare of SLE and more when associated with an increase in anti-dsDNA. If proteinuria is significant and unexpected, it can mean a change in immunosuppression and even renal biopsy if the woman is in the first trimester or in part during the second trimester, although it is only necessary if the clinic and laboratory are discordant. Always keep in mind if the woman is at risk of bleeding after the biopsy and for how long anticoagulation can be delayed in a pregnant woman with intense proteinuria and possibly phospholipid antibodies who, therefore, have a high risk of thrombovenous embolism, since the procoagulant

Clinical measure	Preeclampsia	Lupus nephritis
Time	>20 weeks	>20 weeks
Hypertension	Present	Often present
Urine active sediment	Rare	Common
Onset of proteinuria	Abrupt, after 20 weeks	Abrupt or gradual, anytime
Uric acid	>4.9 mg/dl	<4.9 mg/dl
C3 and C4	Usually normal	Usually low or decreasing
Complement products	Normal	Usually higher
Anti-DNA	Negative or stable	Positive or increasing
Lupus activity	No	Yes
Urine calcium	<195 mg/day	>195 mg/day
Thrombocytopenia	Yes (HELLP)	20% of SLE
Liver function test	May be elevated (HELLP)	Usually normal
Kidney biopsy	Glomeruloendotheliosis	SLE nephritis
sFlt-1/PlGF ratio	Higher	Normal

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and low platelets; SLE, systemic lupus erythematosus; sFlt-1, soluble fms-like tyrosine kinase; PlGF, placental growth factor.

Table 4.
Differentiation of preeclampsia from lupus nephritis flare in pregnancy.

factors are added, pregnancy, nephropathy, SLE activity, and/or aPL. If the risk of having thromboembolism outweighs the benefit of a firm diagnosis, a biopsy should not be done. However, if there is a biochemistry compatible with a flare of lupus, patient's history contains nephritis flares and it is seems that it is going to be repeated; a kidney biopsy could be justified. The distinction of nephritis from lupus of pregnancy preeclampsia (from 26/40 weeks of gestation) can be difficult. In both, there will be an increase in proteinuria, hypertension, generalized symptoms, thrombocytopenia, and kidney damage. In women with isolated preeclampsia, there should be no hematuria, urinary cylinders, a decreasing complement, or increasing anti-dsDNA. However, a flare of lupus nephritis increases the risk of preeclampsia, so, again, distinguishing the two can be a challenge for the clinician. The two treatments are different; preeclampsia requires delivery sooner rather than later, and lupus nephritis requires immunosuppressive treatment. It is not yet a usual practice, but it is likely to be exceptionally useful, measuring angiogenic and antiangiogenic factors, to determine if there is preeclampsia present. Women with APS and SLE who developed preeclampsia had a median of sFlt-1 (tyrosine kinase similar to soluble fms), low placental growth levels (PIGF), and a significantly higher sFlt-1/PlGF ratio, and significantly higher PIGF levels lower compared with women with APS and SLE and without preeclampsia after 12 weeks of gestation. These differences increased with gestational age. The sFlt-1/PlGF ratio became a significant predictor of preeclampsia at 12 weeks, showing the highest levels at 20, 24, and 28 weeks of gestation [8, 9]. Later, the fall of the placental growth factor predicted the appearance of preeclampsia even in women with pre-existing chronic kidney disease. A recent publication highlights the evidence (or more commonly the lack of evidence) for the best use of antirheumatic drugs before and during pregnancy. Women who take azathioprine, hydroxychloroquine, cyclosporine, and tacrolimus can safely breastfeed their babies, so women who take these medications should not be discouraged from breastfeeding.

There are still no safety data on the MMF, so breastfeeding is discouraged if MMF is required. The woman with SLE and pregnancy should be treated as high-risk. At the controls ask for symptoms of the disease to detect SLE flare, and always check the blood pressure to detect preeclampsia. A blood and urine test should be done every quarter to detect biological changes in the complement and anti-DNA that suggest a flare. The fetus must be carefully monitored to detect growth and blood flow. Good multidisciplinary coordination among obstetrician, nephrologists, rheumatologists, and nursing experts is essential for better results.

11. Pregnancy and antiphospholipid antibodies

Pregnancy in women with SLE and aPL-positive courses with obstetric is 80% of cases. The current standard treatment for patients with obstetric includes LDA (75–100 mg/day) and low molecular weight heparin (subcutaneous enoxaparin, dalteparin, nadroparin, or subcutaneous tinzaparin) or unfractionated heparin. These recommendations are based on the results of randomized controlled trials comparing LDA alone or in combination with heparin with APS [7]. Kutteh et al. reported a significant improvement in the rate of live births with LDA and heparin versus LDA alone (80 versus 44%, $P < 0.05$). Rai et al. showed a significantly higher rate of live births with LDA and unfractionated heparin (5000 units) versus LDA alone (71 versus 42%, OR, 3.37, 95% CI, 1.40–8.10). However, no differences were found in the results with the combined treatment versus the LDA in two other randomized trials, both with LMWH, with live birth rates close to 80% in both groups. The heterogeneity in the findings seems to be attributed to the relatively poor results in women who received LDA alone in the two previous studies. In addition, data from observational studies have reported pregnancy success rates of 79–100% with LDA alone in this subgroup of women, although many of these cases had low levels of aPL antibodies. The current recommendation for the treatment of obstetric APS is to initiate LDA plus LMWH at therapeutic doses.

All women should be evaluated for risk factors for venous thromboembolism and should receive postpartum thromboprophylaxis. The Royal College of Gynecology in the United Kingdom, for example, recommends, for aPL-positive women without clinical manifestations of APS, 7 days after thromboprophylaxis of labor, and for women with APS, this extends to 6 weeks. All women with APS can deliver natural light, unless there are obstetric reasons to suggest otherwise. In addition, all women should be encouraged to stop smoking and reduce/discontinue alcohol consumption in accordance with the national pregnancy guidelines. Patients with a recent thrombotic event in the last 3 months, particularly high blood pressure and/or uncontrolled, should be encouraged to postpone new pregnancies. Patients with pulmonary hypertension in general are advised not to get pregnant. Women with previous thrombosis should receive long-term anticoagulation once the risk of postpartum hemorrhage has stabilized. Both AVK (antivitamin K) and heparins are compatible with breastfeeding. With respect to fetal monitoring during pregnancy, the bilateral uterine notch between 23 and 25 weeks of gestation has been shown to be an independent risk factor for the development of early-onset preeclampsia and gestational hypertension. Therefore, the bilateral notch of the uterine artery should be considered in the risk assessment for the development of these pregnancy complications. The evaluation of thrombotic risk should also be considered in patients with a history of obstetric primary health center. Among others, Lefevre et al. demonstrated that patients with obstetric APS have a higher thrombotic risk compared to healthy women (3.3 versus 0–0.5/100 patient years), even if treated with LDA. Similarly, in a 10-year observational study of 1592 women

with pure obstetric SAP and no history of thrombosis, Gris et al. demonstrated that the LA was a risk factor for superficial and superficial venous thrombosis and unprovoked distal and similar results have been demonstrated in other studies.

The current treatment to prevent obstetric morbidity in primary health center (PHC) has improved the outcome of pregnancy at a rate of live births of more than 70%. Given that 30% of women continue to have complications during pregnancy, international groups are currently evaluating different options to improve pregnancy outcomes in women with APS. The additional use of low doses of steroids has been evaluated in refractory APS. It has been suggested that intravenous immunoglobulin improves pregnancy complications in obstetric PHC. Treatment with pravastatin suggests a beneficial role in those women with preeclampsia related to established aPL. In their case series, 11 patients are treated with pravastatin 20 mg/day in addition to the standard treatment, while the controls continued alone with LDA and LMWH. In all patients exposed to pravastatin, signs of preeclampsia, such as blood pressure and proteinuria, improved and signs of placental perfusion remained stable without further deterioration compared to the control group. HCQ has also been evaluated. The HCQ immunomodulator can have beneficial effects not only in the treatment of thrombotic APS but also in the prevention of pregnancy complications [10]. The European randomized controlled multicenter trial "HYPATIA" will evaluate the role of HCQ versus placebo in pregnant women with aPL and, hopefully, provide stronger evidence on the use of HCQ in this context. Complement activation, and therefore a potential role for eculizumab, has also been introduced as a potential target for therapy with APS. The participation of complement activation was investigated for the first time in murine models of pregnancy morbidities related to aPL, and increasing evidence is emerging from both in vitro and in vivo studies. The complement can be activated by binding of the C3 fragment to the Fc receptor of aPL antibodies or by the formation of autoantibodies against C1q, which are frequently detected in patients with APS. The activation of the complement pathway and, consequently, the production of inflammatory molecules such as C5a by aPL, can directly activate platelets and monocytes, inducing the coagulation cascade, which leads to the clinical manifestations of APS. Although in the current literature several case reports describe the successful use of eculizumab in severe cases of APS, such as catastrophic antiphospholipid syndrome (CAPS) and cases of APS and thrombotic microangiopathy, the potential role of eculizumab should be further investigated.

12. Neonatal lupus

Pregnancies in women with anti-Ro and anti-La have an increased risk of developing neonatal lupus (NLS) with or without lupus. Maternal antibodies cross the placental barrier giving a passively acquired fetal autoimmunity. Cutaneous lesions of subacute lupus and hematologic and/or hepatic alterations of the NLS tend to resolve with the elimination of maternal antibodies from 6 to 8 months of age, but the lesion of the developing fetal cardiac conduction pathway can be irreversible. Cardiac injuries include conduction defects, structural abnormalities, cardiomyopathy, and congestive heart failure, but the most serious complication is the development of irreversible complete heart block (CHB), which is associated with a high fetal mortality of 20%. NLS can affect 2% of pregnancies exposed to anti-Ro, but recurrence rates in new pregnancies are 16–20% after a first NLS event. The majority (up to 70%) of the survivors require the insertion of a permanent pacemaker and periodic changes of the same as the child will grow. The CHB may be preceded by lower degrees of driving delays, although it may be sudden onset. Most of the events

occur between 18 and 24 weeks of gestation, but there are later cases, and even post-partum CHB has been described. Early detection and initiation of treatment could stop progression to CHB, but reversal of established CHB has not been reported. Multiple monitoring tools have been proposed for the early detection of cardiac conduction disorder, but fetal Doppler echocardiography remains the most widely used method. The most vulnerable period is between 18 and 24 weeks of pregnancy, so it is recommended in this period of pregnancy to monitor weekly all exposed fetuses, and then every 2 weeks. The detection of an early conduction defect with a prolonged RP interval should indicate the start of a prophylactic treatment to avoid CHB, although we do not have any effective guidelines. The maternal administration of fluorinated corticosteroids and beta-agonists has shown benefits in some specific cases. The treatment of established CHB remains an unresolved problem with minimal benefit with any available approach. The high risk of recurrence in subsequent pregnancies justifies prophylactic therapy for pregnancies at risk. The beneficial effects of IVIg were reported in open studies, but two randomized controlled trials were negative. Both trials have been criticized for their methodology, but the use of IVIg in this context can still be considered as an option. HCQ again deserves special mention. Several studies have shown that HCQ reduces the risk of cardiac NLS in fetuses at risk and possible recurrences. In view of the multiple beneficial effects of HCQ, it is indicated in all pregnant women with lupus and anti-Ro [11].

13. Delivery

Women with SLE have an increased risk of preterm birth. This can occur spontaneously or due to maternal and/or fetal complications, such as a flare of severe lupus, preeclampsia, and FGR. Between 24 and 34 weeks of gestation, the acceleration of fetal lung maturation is essential, with steroids (preferably beta-methasone), regardless of any steroid administered previously. Magnesium sulfate when gestational age is <32 weeks, due to its neuroprotective benefits for the fetus, should be administered in cases of severe preeclampsia. The objective in a pregnant patient with SLE should be a spontaneous delivery at term via the vagina. However, available data have revealed that women with SLE undergo a higher cesarean section (>33%, odds ratio (OR) 1.7, confidence interval (CI) 95% 1.6–1.9). Despite this, it is recommended that cesarean sections be reserved only for obstetric indications, due to their additional risk factor for venous thromboembolism (VTE), blood loss and infection, and repercussions for future pregnancies. Intravenous hydrocortisone may be necessary to overcome the physiological stress of labor if long-term oral steroids, which are very common in SLE, have been taken. The standard prophylactic LMWH should be discontinued at the start of spontaneous delivery and the night before induced labor or elective cesarean section. Regional anesthesia (epidural or spinal) can be performed 12 hours after the last dose of LMWH.

14. Postpartum care

In the puerperium, we must control the activity of the SLE for the detection of flare or coexisting preeclampsia. The treatment for postpartum active SLE is similar to that of nonpregnant women. However, the use of some drugs may have effects on the nursing infant. Therefore, the risks and benefits of continuing to breastfeed should be clarified to the nursing mother. All women who received antenatal LMWH should continue using it for 6 weeks after delivery, in a prophylactic dose, since the puerperium is also a period of increased risk of VTE. In patients with

SLE, postpartum advice to offer safe contraception is particularly important. Good options are long-acting reversible contraception methods. The use of progestogens is only safe and can become an appropriate option. Contraceptives containing estrogen will not use women with aPL or APS, SLE with moderate to severe flare, lupus nephritis, and some other conditions, such as hypertension, smoking, obesity, or previous VTE, since they increase the risk of VTE. In cases of well-defined SLE with stable and/or mild disease, the use of combined oral contraceptives may be indicated. Contraceptive barrier methods have a high failure rate (15–32%) and, therefore, should not be used as a single method.

Abbreviations

SLE	systemic lupus erythematosus
LA	lupus anticoagulant
aCL	anticardiolipin antibody
aβ2GPI	anti-β2 glycoprotein I
aPL	antiphospholipid antibody
HELLP	hemolysis, elevated liver enzymes, and low platelets
sFlt-1	soluble fms-like tyrosine kinase
PlGF	placental growth factor
CYC	cyclophosphamide
LMWH	low molecular weight heparin
ESR	erythrocyte sedimentation ratio
MMF	mycophenolate mofetil
HPA	hypothalamic pituitary axis
AMH	anti-mulleriana hormone
GnRH	gonadotrophic hormone receptor
IUDs	intrauterine devices
IVF	in vitro fertilization
OHSS	ovarian hyperstimulation syndrome
SLEPDAI	SLE pregnancy disease activity index
LAI-P	lupus activity index pregnancy
FGR	fetal growth restriction
NSAIDs	nonsteroidal anti-inflammatory drugs
ACE	angiotensin-converting enzyme
DMPA	depot medroxyprogesterone acetate
SLEDAI	SLE disease activity index
PHC	primary health center
FDA	Federal Drug Association

Author details

Jose Ordi-Ros[1]*, Cristina Sole Marce[2] and Josefina Cortes-Hernandez[1]

1 Internal Medicine, Vall d'Hebron Hospital, Barcelona, Spain

2 Lupus Research Unit, Vall d'Hebron Research Institute, Barcelona, Spain

*Address all correspondence to: jordi@vhebron.net

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