Systemic Lupus Erythematosus and Pregnancy

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that affects predominantly women during their reproductive years. As expected, pregnancy is a common event in these women. Pregnancy was not recommended in women with lupus in the past because of maternal and fetal complications [1, 2]. A better understanding of the disease, the advances of the treatment, and creation of specialized multidisciplinary groups with experience in autoimmune diseases (involving physicians, obstetricians, pediatricians, and midwives) have led to dramatic improvement in disease management and pregnancy outcome over the last 20 years [3, 4]. However, maternal and fetal complications are still present. Risk factors for fetal and obstetric complications are disease activity at the conception and during pregnancy, lupus nephritis (LN), arterial hypertension, positive antiphospholipid antibodies (APLs), and anti-Ro/SSA antibodies [3].

11.1 Preconception Counseling

Fertility in women with SLE seems to be similar to women in the general population, although patients with chronic renal failure, amenorrhea due to previous high cumulative dose of cyclophosphamide (Cyc), and active disease may present reduced fertility. The risk of ovarian failure due to Cyc treatment is related to the cumulative dose of the drug and the administration in women older than 35 years old [5].

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The management of pregnancy in women with SLE should be started before the conception. The preconceptional visit should include a detailed summary of previous obstetric history and chronic organ damage, recent serologic profile, current disease activity and last flare date, medical history and risk factors of interest, and baseline blood pressure and renal function. Main risks for the mother and the baby should be discussed accordingly. High risk factors in lupus pregnancy are adverse obstetrical history, cardiac and renal involvement, pulmonary hypertension, interstitial lung disease, disease activity, high dose of steroid treatment, positivity of APLs and Ro and La antibodies, and multiparity [6]. Women with active lupus should postpone conception until stable disease remission is achieved at least 6 months before conception [7]. Presence of APL and/or APS is associated with maternal thrombosis and fetal mortality and the presence of Ro and La antibodies with congenital heart block (CHB) in 2 % of the babies [7–9, 11]. Severe chronic renal impairment is associated with obstetric complications as preeclampsia and miscarriages [10].

Pregnancy should be contraindicated in some clinical situations (Table 11.1: pregnancy contraindications in SLE). Women with the following conditions should avoid to get pregnant: severe lupus flare or stroke over the last 6 months, pulmonary hypertension, moderate to severe heart failure (ejection fraction of left ventricle <40 %), severe restrictive lung disease (FVC <1 l), severe chronic renal impairment (GFR <35 mil/min), uncontrolled hypertension, and previous severe preeclampsia despite therapy with aspirin plus heparin [7, 9–11, 13]. However, the principal contraindication of pregnancy must be symptomatic pulmonary hypertension because of 30 % of maternal mortality during pregnancy and puerperium [14, 15].

All the medications that patients received to control the disease should be carefully reviewed. Steroids, hydroxychloroquine (HCQ), azathioprine (AZA), and calcineurin inhibitors are considered safe during pregnancy. HCQ is a fundamental treatment in SLE because of their protective properties on activity, damage, long-term survival, and thrombosis. HCQ has been used successfully in pregnancy as steroid-sparing agent, and the discontinuation has been associated with flares of the disease [16–22]. Moreover, its safety profile for both mother and the baby has been widely addressed [16–22]. Methotrexate (MTX), mycophenolate mofetil, and Cyc are teratogenic drugs and they should be avoided and stopped 3 months before the

Table 11.1 Contraindications of pregnancy in SLE

Severe pulmonary hypertension
Severe restrictive lung disease
Heart failure
Uncontrolled hypertension
Severe chronic renal impairment
Severe preeclampsia despite therapy with aspirin plus heparin
Recent stroke (6 months)
Recent lupus flare (6 months)

conception and they should be replaced by AZA to avoid a lupus flare (Table 11.2) [16, 17, 74, 75]. A recent observational study showed that among patients with previous LN, replacing MMF with AZA in women with quiescent LN for pregnancy planning rarely leads to renal flares [75].

Belimumab (BM) and rituximab (RTX) are the most used biological drugs in lupus. The experience of BM in pregnancy is scarce; hence, the current recommendation is to withdraw it at least 4 months before conception. Animal studies showed that BM crossed the placenta, but there is not definitive relationship between BM and congenital abnormalities [76–78]. In the case of RTX, given the maternal indications for its use and the heterogenicity of the reports, until more robust data are available, women should be counseled against pregnancy for 6–12 months after RTX exposure due to the risk of neonatal B cell depletion.

The nonsteroidal anti-inflammatory drugs (NSAIDs) are generally safe in pregnancy if they are used for short limited courses. Their use should be withheld toward the end of pregnancy (>30–32 weeks) due to increased risk of premature closure of baby's ductus arteriosus. At present, there are not reliable data on selective COX-2 inhibitors and they should be avoided [16]. The drugs of choice for managing hypertension in pregnancy are labetalol, methyldopa, and nifedipine and less frequently hydralazine and doxazosin. Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and diuretics are generally contraindicated during pregnancy due to fetal renal impairment and oligohydramnios and increased risk of miscarriages.

Table 11.2 Medications during pregnancy and breastfeeding

	Pregnancy	Breastfeeding
NSAIDs	Yes**	Yes
Hydroxychloroquine	Yes	Yes
Steroids	Yes	Yes
Cyclosporine	Yes	Yes
Azathioprine	Yes	Yes
Mycophenolate mofetil	No	No
Methotrexate	No	No
Cyclophosphamide	No	No
Warfarin	No*	Yes
Heparin	Yes	Yes
Aspirin (low dose)	Yes	Yes
Anti-TNFα	Yes	Yes
Rituximab	No	No
Abatacept	No	No
Belimumab	No	No

NAIDs Nonsteroidal anti-inflammatory drugs, *TNFα* tumor necrosis factor alpha, **(avoid after 32 weeks), warfarin* (could be given after 1st trimester)

11.2 Activity Disease in Pregnancy

Pregnancy is considered a high-risk time for lupus patients, as flares during pregnancy have been described. However, whether or not pregnancy increases the risk of lupus flare is still an unsolved question. Several prospective controlled studies have shown an increase in lupus flares during pregnancy [22–24], while other studies showed opposite results [25–28]. However, the lupus flare rate during pregnancy was around 50 % in all the studies. The risk of flare appears to be dependent on the disease activity 6–12 months prior to conception and previous treatment with HCQ [18, 24, 29]. However, recent studies have shown a reduced frequency of lupus flares when compared to old studies [30, 31].

Distinguishing pregnancy-related signs and symptoms from certain lupus features may sometimes be difficult, as they can mimic each other. Assessment by experienced physicians is of great importance in order to ensure a correct clinical judgment. Fatigue, arthralgia, hair loss, dyspnea, headaches, malar and palmar erythema, edema, anemia, and thrombocytopenia represent some of the most ambiguous manifestations.

In pregnancy, erythrocyte sedimentation rate (ESR) is usually raised; hence it may not be valid as an activity marker. Serum C3 and C4 levels also rise in pregnancy due to increased liver production, so even in women with active lupus, they may remain within normal range. Relative variation rather than absolute levels of C3 and C4 should be taken into consideration. A drop of 25 % or more in serum complement levels should be taken into consideration [32]. Several activity indexes for pregnancy have been used for research purposes; however, physicians should take therapeutic decisions by clinical judgment [33, 34].

Lupus flares during pregnancy and postpartum are normally non-severe, characterized by articular, dermatological, and mild hematological involvement and are usually well controlled with HCQ and short-term introduction or increase in steroids. Nonetheless, severe flares with major organ involvement may occur, and the patients may require high doses of steroids, pulses of steroids, and early treatment with AZA to spare steroids [3, 16, 32].

11.3 Lupus Nephritis and Pregnancy

Active LN at conception confers a higher risk of flare during pregnancy, and even women with LN in remission have an increased risk of flare [33–44]. In contrast, patients with no previous renal involvement are at the lowest risk. Arterial hypertension and renal impairment are important prognostic factors in LN. As a result of increased renal blood flow in pregnancy, glomerular filtration rate (GFR) increases by more than 50 %, leading to reduce creatinine level. Increased tubular flow may increase urine protein leakage; thus levels up to 300 mg/day are considered normal in pregnancy. In patients with permanent significant protein loss due to previous LN, proteinuria may elevate throughout pregnancy with or without being indicative of active nephritis. This phenomenon could explain the variable incidence of renal

flares (8–64 %) in different studies, while the renal flares with renal impairment are between 0 % and 23 % [33–41]. Moreover, different definitions of lupus flare could also explain it. Moroni et al. defined nephritic flare as an increase more than 30 % of serum creatinine plus pathologic urine sediment and proteinuric flare as an increase in proteinuria level (more than 2 g/day if the basal level was less than 3.5 g/day and the double value if the basal level was in nephrotic range) without creatinine serum modification. The authors identify a rate of 25 % of lupus flares with this definition [40]. Moderate and severe renal insufficiency at the conception increases the risk to develop maternal hypertension and premature delivery. In patients with mild and stable renal impairment and control of blood pressure, the risk of progression to end-stage renal failure is low. On the other hand, if the patients have moderate renal impairment (serum creatinine between 1.4 and 3.0 mg/dl), the prognosis of renal function is worse. Patients with severe renal insufficiency have a bad maternal and fetal prognosis [45, 46]. A recent meta-analysis evaluated 37 studies in 2,751 pregnancies with LN and they found the presence of APL and the LN increased the risk of maternal hypertension and premature delivery [47]. However, another retrospective study analyzed patients with and without LN, and they found an increased number of renal lupus flares but the same outcome in terms of fetal survival, premature delivery, preeclampsia, and weight of birth [86].

The early diagnosis of lupus flare is very important for the treatment and prognosis. The irreversible renal insufficiency has been reported between 0 % and 10 % and persistent hypertension in around 13 % of patients [35, 36, 40].

Preeclampsia is defined as the presence of arterial hypertension plus proteinuria after 20 weeks of pregnancy. Patients with SLE, LN, and/or APL present higher risk to develop preeclampsia compared with the general population [48, 49]. Differentiating preeclampsia from LN may not be straightforward, as both may include hypertension, raising proteinuria, edema, renal function impairment, and thrombocytopenia, and sometimes both may overlap. Table 11.3 shows useful findings to differentiate preeclampsia from LN. Active urine sediment, the increase in serum creatinine level, and the positivity of anti-dsDNA antibodies and lower levels of complement could suggest a renal flare [50].

Table 11.3 Differential diagnosis of preeclampsia and lupus nephritis

	Preeclampsia	Lupus nephritis
Blood pressure	High	Normal/high
Platelets	Low/normal	Low/normal
Complement	Normal	Low
Anti-dsDNA	Normal	High
Uric acid	High	Normal
Creatinine level	Normal/high	Normal/high
Hematuria	Present (+/–)	Present
Active urine sediment	No	Yes
Extrarenal SLE activity	No	Yes
Steroid response	No	Yes

Lupus flare treatment includes steroids, pulses of steroids, and AZA. Cyc and MMF are contraindicated during pregnancy and they should be avoided [16, 17]. Tacrolimus is a calcineurin inhibitor and prevents the activation of T cells and the transcription of IL-2, and it can be used during pregnancy [74]. Webster et al. reported the use of tacrolimus in 9 LN patients for renal flares or maintenance treatment [79].

Low-dose aspirin started before 16 weeks of gestation reduces the risk of preeclampsia and its complications [51]. Taking into account its low side effects and recent data suggesting its benefit, antiplatelet therapy for the prevention of preeclampsia is recommended in patients with SLE with or without APL. Some studies have evaluated the use of low-dose aspirin plus heparin in patients with severe preeclampsia in previous pregnancies with positive results [52–54]. However, heparin is not recommended for prevention of preeclampsia, and prospective studies should be done to confirm these results.

11.4 Antiphospholipid Syndrome and Pregnancy

APLs are found more frequently in patients with SLE (30–40 %) than in the background of population (1–5 %) and represent the major risk factor for poor obstetric outcome [55, 56]. Several studies have identified APL carrier women at increased risk of developing preeclampsia, IUGR, prematurity, and fetal loss during pregnancy [8, 11, 57]. Recurrent pregnancy loss occurs in more than 50 % of women with high titers of APL [11]. A meta-analysis studied the relationship between different APLs (LA, ACL IgG, ACL IgM, and anti-B2 glycoprotein I antibodies) and recurrent pregnancy loss. LA, ACL IgG, and ACL IgM had a strong association with recurrent pregnancy loss before 24 weeks of pregnancy and ACL IgG with early miscarriages (before 13 weeks of pregnancy) [58].

Treatment of women with obstetric APS is still the subject of controversy and should be individualized, as most of the evidence is based on observational studies. Current recommendations include low-dose aspirin alone or in association with prophylactic low-molecular-weight heparin (LMWH) for women with recurrent early miscarriages (<10 weeks of gestation) and low-dose aspirin plus prophylactic LMWH for women with previous fetal death (>10 weeks of gestation) and/or preterm delivery (<34 weeks of gestation) [11, 59–64] (Table 11.4). All women with APL positivity should receive low-dose aspirin before the conception to decrease the risk of miscarriages and preeclampsia [49, 51, 64].

All women should be assessed regarding risk factors of venous thromboembolism prior to conception and periodically throughout pregnancy and should receive thromboprophylaxis accordingly. Anticoagulation doses of LMWH are indicated for patients with history of thrombosis, as warfarin is contraindicated in the first trimester of pregnancy because of its fetal effects [65]. All women with APL should receive at least prophylactic LMWH for 7 days after delivery in the absence of other risk factors. Some experts recommend extending this treatment for 4–8 weeks postpartum [65]. In all the patients under treatment with heparin, calcium and vitamin D

Table 11.4 APS treatment in pregnancy

Clinical manifestation	Recommendations
APL(+) without thrombosis or obstetric morbidity	Low-dose aspirin (no evidence)
APS: early recurrent miscarriages	Low-dose aspirin or aspirin + heparin
APS with history of fetal death, preeclampsia, IUGR	Low-dose aspirin + LMWH prophylactic dose during pregnancy and puerperium
APS with venous thrombosis	Warfarin is avoided in the 1st trimester
	Low-dose aspirin + LMWH (anticoagulation dose after 16 weeks)
APS with arterial thrombosis	Warfarin is avoided in the 1st trimester
	Low-dose aspirin + LMWH anticoagulation dose during pregnancy and puerperium
APS recurrent pregnancy loss in spite of aspirin + LMWH	Steroids, HCQ

for prevention of osteoporosis should be considered [65, 66]. On the other hand, warfarin and heparin can be used during breastfeeding.

11.5 Neonatal Lupus

Neonatal lupus (NL) is associated with the presence of maternal anti-Ro and anti-La antibodies that are present in 30 % of lupus patients and in Sjogren's syndrome. Congenital heart block (CHB) is the most severe complication of NL and happens in around 2 % of babies born to anti-Ro/La-positive mothers. This risk increases up to 18 % if the mother has already had a child affected by CHB and up to 50 % if she has had two children affected [12, 67, 68]. The risk of perinatal death among affected children is approximately 10–20 %, and most of the surviving children need a permanent pacemaker.

CHB normally develops between 16 and 24 weeks of gestation and can be detected by fetal low heart rate (<60 beats per minute). Early diagnosis is crucial for correct management in CHB. Ultrasound is the accepted technique for fetal CHB diagnoses. Current recommendations include serial fetal echocardiograms between 18 and 28 weeks of gestation for pregnant women with anti-Ro/La antibodies. When the complete CHB is detected, it is not reversible. Some authors suggest dexamethasone treatment as effective in second-degree CHB [69].

The PR Interval and Dexamethasone Evaluation (PRIDE) study was designed to evaluate the efficacy of dexamethasone treatment to prevent or revert the recently diagnosed CHB. This study also evaluated if first-degree heart block was a predictor factor to progress to complete heart block. They found the prolongation of PR interval did not predict complete CHB. The presence of echodensities and tricuspid regurgitation were early signs of heart damage [70].

In a murine model, treatment with intravenous immunoglobulins (IVIGs) was proved to inhibit anti-Ro/La antibody placental transfer and their consequent fetal

heart damage. Nevertheless, two multicenter prospective studies failed to reduce the risk of CBH in women, with a previously affected baby, treated with IVIG during pregnancy [71, 72]. A recent multicenter case-control study suggested that, in mothers with anti-Ro/La, exposure to HCQ during pregnancy may decrease the risk of fetal development of CHB [73]. Recently, two other studies showed a decrease in recurrences of CHB in mothers who were exposed to HCQ [80, 81, 87]. These results should be evaluated in future studies.

11.6 Pregnancy Management

Prepregnancy counseling; risk assessment; multidisciplinary approach; antenatal and postnatal management plan, together with experienced team; and early recognition of signs related to SLE complications are essential cornerstones for both maternal and fetal successful outcomes. The preconceptional visit should include a summary of previous obstetric history and chronic organ damage, recent serology profile (APL, anti-Ro/La, anti-dsDNA, complement), current disease activity and last flare date, medical history and risk factors of interest (diabetes, hypertension, cardiac and cardiovascular problems, nephropathy, thyroid function, detrimental habits, and their complications), and baseline blood pressure, urine analysis, and renal function [82]. Anomaly scan and uterine arterial Doppler are recommended around 20 weeks of gestation, and the latter should be repeated around the 24th week if abnormal. Abnormal wave forms are good predictors of preeclampsia, whereas normal results are related to good obstetric outcomes. Ultrasound scans (including biophysical profile and amniotic fluid volume assessment) around 28–30 weeks and 32–34 are recommended. Regular umbilical artery Doppler should be performed with the previous scans, as their abnormal values are predictors of mortality and risk of fetal compromise. Additional scans may be indicated depending on previous obstetric history and the progress of pregnancy [83–85].

Every visit should include urine analysis and maternal assessment with special attention to hypertension and other features of preeclampsia. Women with previous renal and/or hypertensive diseases should have more frequent regular blood pressure checks. Confirmation by protein/creatinine ratio is mandatory in case of positive urine dipstick. Regular blood tests including full blood count, liver function tests, renal profile, anti-dsDNA and complement every 4–8 weeks are recommended. All women on steroids and those with high risk factors of diabetes should have a glucose tolerance test around 24–28 weeks of gestation in order to exclude gestational diabetes and avoid further obstetric risk. All women should ideally take folic acid 12 weeks before the conception and calcium and vitamin D supplements for women on steroids and heparin treatment to prevent osteoporosis [82].

Conclusions

SLE is no longer considered an obstacle to pregnancy. Some fetal and obstetric complications can be predicted and in some cases prevented. A tight control of patients should be performed before and after conception. These patients should

be managed by a multidisciplinary team, including at least a rheumatologist and an obstetrician, thus allowing an improvement of maternal and fetal prognosis.

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