Management of the High-Risk Lupus Pregnant Patient
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Systemic lupus erythematosus (SLE) is a disease predominantly affecting women in their reproductive years. Its frequency is 1 per 700 women with a peak incidence at around age 30 [1]. Of deaths from SLE, 36.4% occur among persons aged 15 to 44 years [2]. The prevalence of death in SLE pregnancy has been reported to be 0.05% [3]. Given the potential lethality, all pregnant women with SLE should be considered at high risk.

Management of SLE in pregnancy is a multidisciplinary effort including a rheumatologist, an obstetrician with experience in management of patients with SLE, and, if indicated by the patient’s renal status, a nephrologist. This chapter covers the obstetric management of these patients. Management of SLE flares during pregnancy and those patients at risk for in utero congenital heart block will be covered in other articles of this issue, as will predictors of pregnancy success and loss.

Initial assessment

The initial assessment must always be a collaborative effort between the obstetrician and the rheumatologist. This must include a comprehensive and up-to-date assessment of the activity of lupus, organ damage, laboratory tests, and medication exposure.

The initial history should include the duration and current activity of the patient’s disease. If she is in remission, how long the remission has lasted should be documented. Typical signs or symptoms the patient is known to experience during exacerbations of her disease should be recorded. Organ system involvement with special emphasis on the kidneys and thrombocytopenia should be explored with the patient. Current and past therapy should

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be reviewed. The patient’s past obstetric history and the timing of past pregnancy with regard to onset of her lupus should be noted.

The physical examination should be focused on establishing accurate pregnancy dating and baseline blood pressure. The dating should be confirmed by an early obstetric sonogram.

Laboratory testing should include the standard evaluation for other pregnant women [4]. Additional baseline tests should include complement studies (C3, C4, CH50), anti-dsDNA, anticardiolipin antibodies, lupus anticoagulant (Russell viper venom time), anti-SSA and SSB (Ro and La), microscopic urinalysis, and a 24-hour urine collection to determine total protein, total calcium, creatinine clearance, and protein-to-creatinine ratio.

Once all data are available, the rheumatologist and the obstetrician can make a joint assessment of the patient’s status and plan her ongoing care. The rheumatologic follow-up will be outlined in another chapter in this issue. The obstetric follow-up is based on standard prenatal care, which is modified based on the patient’s specific risks. An outline of standard prenatal care can be found in Reddy and Rossiter [4].

**Maternal health**

Interactions between SLE and pregnancy include the overall activity of lupus and pregnancy outcome, the effect of lupus nephritis on pregnancy, the effect of pregnancy on the progression of lupus nephritis, and the differentiation of hypertension related to lupus nephritis from preeclampsia. The issue of lupus flares and pregnancy will be covered elsewhere in this issue.

**Lupus nephritis**

The prevalence of chronic renal disease among pregnant patients with SLE in a California population-based study was 7.8% versus 0.1% in controls [3]. Lupus nephritis appears to be more active during pregnancy. Most increases in lupus nephritis are mild and reversible [5–8]. However, about 12% of patients will have irreversible progression of their renal disease [9]. In patients starting pregnancy with moderate renal failure, as reflected by a serum creatinine level of 1.4 mg/dL or greater, there is a greater decline in renal function than would be expected for a similar time period in a non-pregnant patient [10]. For those patients receiving immunosuppressive therapy for their lupus nephritis, pregnancy does not appear to accelerate their disease progression [11].

**Hypertension—preeclampsia versus lupus nephritis**

Preeclampsia occurs after 20 weeks and is defined in a previously normotensive woman as a blood pressure of 140 mm Hg systolic or higher or 90 mm Hg diastolic or higher with proteinuria defined as a urinary excretion
of 0.3 g of protein or higher in 24 hours [12]. Preeclampsia is more common in patients with SLE. Reviews quote rates of 20% to 30% [13]. A case-control study from the Hopkins Lupus Cohort showed a preeclampsia rate of 15% versus 3% in unaffected relatives (\( P < .0001 \)) [14]. A population-based study from California reported that hypertensive complications of pregnancy occurred in 2.9% of patients with SLE, but only in 0.4% of controls (\( P < .0001 \)) [3]. However, in the same study, hypertensive complications were the indication for cesarean delivery in 23.5% of SLE patients but only 5.3% of controls (\( P < .001 \)) [3]. In SLE patients with renal involvement, preeclampsia has been reported to occur in one third of the patients entering the third trimester [15].

The different rates of preeclampsia that have been reported most likely are related to selection bias in the case series. Hypertension can be associated with lupus renal involvement, and because preeclampsia can be superimposed on chronic hypertension, the diagnosis often is difficult. Normal blood pressure changes seen in pregnancy further complicate the diagnosis. Blood pressure in pregnancy tends to be lower starting in the first trimester and increases at term [16]. This normal change in blood pressure must be taken into account when a chronic hypertensive patient experiences an increase in blood pressure at term.

In SLE patients with renal involvement and fixed glomerular lesions, the increased glomerular filtration rate seen with pregnancy [16] may lead to increased proteinuria, which is not preeclampsia related [1]. Thus, an increase in blood pressure and proteinuria may occur at term, making the diagnosis of preeclampsia more difficult.

Preeclampsia occurs after 20 weeks’ gestation, except in the presence of multiple gestation or trophoblastic disease [12]. Therefore, it is likely that an increase in blood pressure in the first half pregnancy is not preeclampsia.

Changes in some laboratory measures may be helpful in the differential diagnosis. Whereas in normal and preeclamptic pregnancies, C3 and C4 increase near term, they tend to decrease with increased lupus activity [17]. Decreases in CH50 have also been associated with increased lupus activity, but not preeclampsia [1]. Changes in complement activation may be especially useful in a patient with a personal history of decreased complement markers during periods of increased lupus activity.

Normal pregnancy leads to increased calcium excretion. This normal increase in urinary calcium excretion is not seen in preeclampsia. Using a cutoff of below 195 mg/24 hours for urinary calcium excretion, the sensitivity for prediction of preeclampsia is 86% with a specificity of 84% [18].

None of these differences between increased renal lupus involvement versus associated hypertension and preeclampsia are definitive. Because the treatment for preeclampsia is delivery, when the patient is at term and the diagnosis is uncertain, the delivery should be performed. If this fails to improve the situation, the infant will not have been harmed and therapy can proceed for the mother. Each patient’s care must be individualized.
Pregnancy outcome

Pregnancy loss

Pregnancy loss in patients with SLE is decreased if the patient has been in remission for 6 to 12 months before conception [1]. Patients with SLE experience pregnancy loss at a greater rate than the general population [3,19,20]. They experience a 4.7-fold increase in spontaneous abortion after the diagnosis of SLE compared with their reproductive history before the SLE diagnosis [21].

The gestational age at which pregnancy loss occurs in patients with SLE is difficult to determine, because most reports are from highly selected referral populations. Second trimester losses and stillbirths are most consistently reported to be increased [3,13,19,22], although increased losses after 10 weeks have also been reported [23]. Because 10 weeks represents a better divide between embryonic and fetal losses, this may represent a more valid cutoff point. In one study that included the distribution of losses in the first and second trimester, 45% occurred in the first trimester and 55% occurred in the second trimester [24]. This indicates a disproportional number of second trimester losses when compared with the general population.

The obstetric history is a strong predictor of outcome in subsequent pregnancies. When an SLE patient has had a previous pregnancy loss, she is at increased risk of subsequent losses, independent of other risk factors for loss [13,19,22].

Pregnancy loss is increased with renal involvement with lupus [8,15]. Hypertension, which may be associated with renal lupus or preeclampsia, is associated with pregnancy loss [1,25]. First trimester hypertension is associated with both pregnancy loss before 20 weeks and stillbirth [25]. Preeclampsia, which is a primary risk factor for stillbirth [12], also increases the stillbirth rate for patients with SLE above that seen with SLE alone [1].

Additional predictors of loss, including lupus activity and secondary antiphospholipid syndrome, are discussed elsewhere in this issue.

Fetal growth restriction

The rate of intrauterine growth restriction (IUGR) in pregnancies complicated by SLE is estimated to be as high as 30% by a recent review [13]. This increased risk of IUGR is seen even with mild disease [22]. Renal involvement with lupus increases the risk of impaired fetal growth [8,15]. Small-for-gestational-age infants occur at all gestational ages, but are more common in those infants born prematurely [20]. A large population-based California study confirmed this increase in IUGR [3]. It also found that, at any gestational age, the birth weight for the SLE patient’s baby was lower than that of control infants. This difference persisted when the analysis was repeated, controlling for hypertension and renal disease.
Therefore, SLE has a primary effect on in utero fetal growth, irrespective of activity of disease or complications.

*Prematurity*

After the development of SLE, the occurrence of preterm birth increases 6.8 times compared with the same patient’s reproductive history before the onset of their disease [21]. Although the reported rates vary widely, prematurity is increased in patients with SLE [22]. An estimated average rate is 44% [22]. Active lupus increases the rate of prematurity [1,22,24,26]. Term birth decreases from 61% with no or mild lupus activity to 26% with high-activity lupus (\(P < .001\)) [26]. Other complicating factors that contribute to prematurity include preeclampsia, hypertension, non–high school graduation and Raynaud’s phenomena [1,14,24].

Many of the rates sited for prematurity may be biased because of the referral basis of most reported series. A large birth certificate–based population study showed a 21% prematurity rate versus 4.2% rate in control patients (\(P < .001\)) [3]. Additionally, the average length of gestation was 13 days shorter in lupus patients (\(P < .0001\)). The cause of prematurity in lupus includes those patients delivered for maternal indications and fetal distress. However, these are not the majority of the cases. Most reports do not list the cause of preterm delivery. One report indicated that idiopathic preterm labor was the most common cause [15]. A later report implicated premature rupture of the amniotic membranes as the instigating cause for preterm labor and delivery [27]. In that study, the incidence of premature rupture of the amniotic membranes was statistically increased between 34 and 36 weeks’ gestation and after 36 weeks’ gestation. The prematurity associated with spontaneous preterm delivery was therefore primarily in the late preterm range (34 to 36 weeks’ gestation), which carries a better prognosis for the neonate.

*Individualized therapy*

*General*

Prenatal care for patients with SLE begins with the standard prenatal care recommended jointly by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists [28]. This standard care should be modified for SLE patients because of their increased risks of pregnancy loss, intrauterine growth restriction, and preeclampsia. Additionally, collaborative monitoring of lupus activity between the rheumatologist and the obstetrician must be included. This part of the prenatal care is covered in the article by Clowse, found elsewhere in this issue.

Standard prenatal care includes visits every 4 weeks up to 28 weeks, then every 2 to 3 weeks until 36 weeks, and then weekly until delivery [28]. These visits include evaluation of the woman’s blood pressure, weight gain, uterine
size for progressive growth consistent with the estimated date of delivery, fetal heart rate, and urinalysis for the presence of protein. Tests of fetal well being are not recommended in the routine pregnancy but are indicated for patients with SLE [28].

Because of the previously discussed increased risks of preeclampsia, hypertension, intrauterine growth restriction, and pregnancy loss, standard prenatal care needs to be modified in several ways [12,28,29]. The number of visits needs to be increased starting at 20 weeks. Because preeclampsia occurs after 20 weeks, obstetrical visits are increased to every 2 weeks at this point and become weekly at 28 weeks. The monthly 24-hour urine collections performed as part of the rheumatologist’s visits, discussed under surveillance for lupus flares elsewhere in this issue, can also be used for the surveillance for preeclampsia [12].

Surveillance for fetal growth can be conducted by serial obstetric sonography [12,29–31]. This is especially important in the patients who have chronic hypertension [30] or in whom preeclampsia has developed [12]. A baseline sonogram early in pregnancy to confirm gestational dating is recommended. The most precise measurement can be achieved by crown rump measurement in the first trimester [31]. This should be followed by an anatomic survey looking for fetal anomalies at 16 to 20 weeks’ gestation. This second examination will also allow for the first growth follow-up. Subsequent scans should be at 4-week intervals [31]. In the setting of diagnosed preeclampsia or intrauterine growth restriction, the interval can be reduced to 3 weeks [12,29]. However, an interval of 2 or fewer weeks is not recommended, because, at shorter intervals, measurements may overlap causing errors in fetal weight estimation [31]. It is important to measure amniotic fluid volume at each growth sonogram. In the absence of ruptured amniotic membranes, decreased amniotic fluid is a sensitive indicator of growth failure [31].

Fetal surveillance because of the risk of fetal loss is an important part of the prenatal care of SLE patients. Fetal surveillance for these patients includes the nonstress test (NST), the biophysical profile (BPP), and fetal umbilical artery Doppler velocimetry [32]. Testing is usually started at 26 to 28 weeks and continued weekly until birth. The frequency of testing may be increased depending the patient’s clinical course. These tests need to be interpreted with care at earlier gestational ages.

The NST and BPP were developed for full-term or near-term fetuses. The NST evaluates the fetal heart rate response to fetal motion and relies on the development of the autonomic nervous system control over heart rate. Maturation of this control occurs between 28 and 32 weeks’ gestation [33]. The NST is a 20-minute period of observation using the external fetal monitor in which two accelerations in the fetal heart rate lasting 15 seconds and with a maximum increase of 15 beats per minute at term are considered a positive result and thus a reassuring assessment of fetal status. Between 28 and 32 weeks, the criteria for acceleration are an increase in fetal heart rate lasting
10 seconds with a maximum increase of 10 beats per minute [32]. Below 28 weeks this test is not consistently reliable.

The BPP includes 5 specific measure of the condition of the fetus, each of which, if present, contributes two points to an overall score [32]. One measure used is the NST, which has the gestational age consideration listed above. The other measures require up to a 30-minute real time two-dimensional ultrasound examination to evaluate the fetus. Three of the remaining measures are of fetal activities. Fetal breathing motions are assessed by observing rhythmic fetal chest motion of at least 30 seconds in duration. Fetal body or limb movements are assessed by documenting at least four discrete body movements. Fetal tone/posture is assessed by observing the presence of extension/flexion of the fetal limbs. The final parameter measured is an amniotic fluid pocket free of umbilical cord of greater than 2 cm depth. The maximum score is 10 for more than 28 weeks and 8 for less than 28 weeks. Values of six or less are considered nonreassuring. It is useful beginning at 26 weeks.

Fetal umbilical artery Doppler velocimetry has established normal ranges and should only be used in combination with other tests [32]. It is especially useful to predict prognosis in patients with IUGR [29,31]. The use of fetal umbilical artery velocimetry is associated with a 38% reduction in the risk of fetal death when combined with other tests of fetal well being [34]. However, this test needs to be interpreted in the context of gestational age, because absent end diastolic flow, which is abnormal at near term and at term, is a normal finding in early gestation [32].

In those patients at risk for fetal congenital heart block, caused by SSA (Ro) and SSB (La) antibodies, as discussed in the article by Buyon in this issue, additional specific testing is required. This fetal condition occurs after 16 weeks. Although 53% of the time it has onset between 16 and 24 weeks, it can have onset as late as 38 to 40 weeks [35]. Therefore, screening should begin at 16 weeks and continue weekly until delivery. Screening can be done by fetal m-mode echocardiography [36], which allows for early diagnosis and in utero therapy for this condition as discussed elsewhere in this issue.

Antiphospholipid antibodies/lupus anticoagulant

As outlined elsewhere in this issue, antiphospholipid syndrome, defined as the presence of anticardiolipin, anti-beta 2 glycoprotein I, or lupus anticoagulant is a predictor of poor pregnancy outcome in pregnant women with SLE. Although in nonlupus patients antiphospholipid syndrome has more often been associated with early losses [37–41], in lupus patients it has been more associated with second and third trimester losses and stillbirths [1,3,13,14,19,22,23,42]. This may be an artifact of how these series have been collected, because, in general, the nonlupus series have been from populations with recurrent spontaneous early losses, whereas the lupus studies have concentrated on SLE patients who became pregnant. The lupus
studies may be undersampled for early losses, because many women register for pregnancy after the first trimester. Because it is reasonable to assume lupus is not protective against early loss from antiphospholipid syndrome, it is prudent to begin therapy as soon as pregnancy is diagnosed.

In patients without a history of thrombosis, the treatment during pregnancy is to decrease the risk of pregnancy loss. The current recommendation in this patient group is to treat with prophylactic subcutaneous doses of heparin or low-molecular-weight heparin and low-dose (81 mg) aspirin [43]. The lowest stillbirth rates are reported with this combination [13]. Trials with aspirin alone have not shown a benefit [44,45], although a small additional affect of aspirin could not be ruled out in a recent large review [45].

Prophylactic unfractionated heparin is administered at 5000 units at 12-hour intervals. Because of the alteration in low-molecular-weight heparin’s pharmacokinetics [46], 12 hour dose administration is indicated. The dose for enoxaparin is therefore 30 mg every 12 hours and that for dalteparin sodium is 2500 international units every 12 hours. Because of concerns of the risk of epidural hematoma formation with the use of conduction anesthesia for delivery, use of low-molecular-weight heparin is converted to unfractionated heparin 4 weeks before the anticipated delivery date, and use of unfractionated heparin is discontinued at the onset of labor or 8 hours before planned cesarean delivery. Postpartum, many hematologists recommend continuing the patient on 81 mg of aspirin per day indefinitely and continuing the woman on heparin for 6 weeks postpartum.

In patients with a history of thrombosis, full anticoagulation is indicated and should be done with heparin or low-molecular-weight heparin [43]. Subcutaneous injection of either unfractionated or low-molecular heparin may be used. In the third trimester, unfractionated heparin will need to be used at an 8-hour injection intervals to maintain therapeutic levels as half-life decreases in pregnancy. The target for anticoagulation with unfractionated heparin is an activated partial thromboplastin time (aPTT) with international normalized ratio (INR) of 2.5.

As previously discussed, low-molecular-weight heparin should be administered subcutaneously in pregnancy every 12 hours. Therapeutic dose administration for the various low-molecular-weight heparins should start on a weight basis: enoxaprin sodium 1 mg/kg every 12 hours or dalteparin sodium 100 IU/kg every 12 hours. To assure adequate therapeutic levels, peak (measured 3 to 4 hours after the dose) and trough (drawn within 1 hour of the next dose) anti-Xa levels should be drawn. The peak should not be greater than 1.2 anti-Xa units and the trough should be more than 0.5 anti-Xa units.

Therapeutic low-molecular-weight heparin should be converted to unfractionated heparin because of the risk of epidural hematoma with conduction anesthesia for delivery 4 weeks before the estimated date of delivery. Except in cases of extreme risk, heparin use is discontinued during labor
for those patients and then low-molecular-weight heparin alone or in combination with warfarin may be restarted 12 hours after delivery. Although the heparin therapy is interrupted for labor and delivery, mechanical thromboprophylaxis with supportive stockings and lower extremity intermittent compression devices should maintained.

*Lupus nephritis*

When managing lupus nephritis in pregnancy, care should be coordinated with the patient’s rheumatologist and nephrologist. In general, deteriorating renal function is a greater threat to the fetus than the therapy for lupus nephritis. Therefore, the patient should be treated in a similar manner regardless of whether she is pregnant.

The preferred corticosteroid is prednisone because it is inactivated by the placenta. Prednisone is the mainstay for therapy in pregnancy for lupus nephritis. However, prednisone treatment for lupus is not adequate to induce fetal lung maturation. If fetal lung maturation must be induced before preterm delivery, a specific course of betamethasone or dexamethasone must be added [47].

If hydroxychloroquine is being used to maintain remission, it should be continued during pregnancy. Its discontinuation increases lupus activity and it has been used safely in pregnancy without adverse fetal affects [48–51].

Diuretics are usually not used during pregnancy because they can decrease intravascular volume, the expansion of which is a part of normal pregnancy [52]. If loop diuretics are needed to maintain renal function, they should be continued. However, they should not be used as primary therapy for blood pressure control [52]. Furosemide is the loop diuretic with the best track record for treatment of chronic renal failure in pregnancy. It poses a low risk to the fetus [53].

Among the immunosuppressive drugs, the one with the most experience in pregnancy is azathioprine. It does not appear to be a human teratogen, but it is associated with intrauterine growth restriction [53]. This association cannot be characterized as causal, because of the confounding affects of the underlying disease and concurrent other drugs. In lupus nephritis its benefit out weighs the risk.

Cyclophosphamide can be used to treat acute worsening of lupus nephritis unresponsive to other therapy. Because of its teratogenic potential, it should only be used after the first trimester unless the mother’s life is threatened [53].

In patients with rapidly progressing renal failure, emergency hemodialysis should be considered in consultation with the patient’s nephrologist. This is especially true for those patients who have had a renal transplant and are experiencing acute rejection. Discussion of this group of patients is beyond the scope of this chapter.
Treatment of hypertension

Treatment of chronic hypertension in pregnancy is reserved for patients with diastolic blood pressures greater than 90 mm Hg. Controlling chronic hypertension with antihypertensive medications to achieve a blood pressure of less than 140/90 mm Hg is safe in pregnancy but does not improve perinatal morbidity or mortality nor does it reduce the risk of intrauterine growth restriction when compared with placebo treatment [54]. Treatment of chronic hypertension during pregnancy is to benefit maternal health [30].

The preferred agents for treatment of hypertension in pregnancy are methyldopa and labetalol [30]. Both have long histories of safety in pregnancy. They can be used in the standard nonpregnant doses during pregnancy.

Hydralazine also has a long track record of safety in pregnancy [12]. Because of its ability to produce a lupuslike syndrome when used for more than 6 months and the possible confusion between this drug-induced syndrome and an exacerbation of lupus, it is in general not used in pregnant SLE patients for chronic therapy.

Angiotensin-converting enzyme (ACE) inhibitors are not used during pregnancy, because they have been associated with irreversible renal damage in the fetus and fetal loss [53]. Because of their similar mechanism of action, angiotensin II receptor blockers also are not used during pregnancy.

As discussed above, diuretics are not used as primary therapy for chronic hypertension in pregnancy. Loop diuretics may be used if needed to support renal function in lupus nephritis.

If the patient does not respond to therapy with the preferred agents or cannot tolerate such therapy because of adverse drug reactions, second-line agents should be considered. Although nifedipine is a teratogen in some animal models, it has been used without problems in human pregnancy [53]. Beta blockers can also be used, although they have been associated with intrauterine growth restriction [30]. It is unclear whether the association with intrauterine growth restriction is causal or is caused by the underlying disease. The association between intrauterine growth restriction and atenolol is, however, strong enough that it has been recommended that it not be used [30].

Summary

A pregnancy in a patient with SLE is at high risk for maternal complications of pregnancy and pregnancy wastage. However, most patients can achieve a live birth. This can be achieved by close coordination of care between the patient’s rheumatologist, obstetrician, and, in the case of renal involvement, her nephrologist.
References


