Management of Pregnancy in Women with Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) predominantly affects women of childbearing age, and the management of pregnant patients with SLE is challenging because pregnancy can aggravate SLE and vice versa. Furthermore, the drugs used to treat SLE can adversely affect the fetus. Accordingly, pregnancy should be planned in advance in women with lupus, and careful planning and treatment are required to care for women with lupus who become pregnant. This article reviews the pre-pregnancy evaluation and management of pregnant women with SLE with the aim of providing general guidelines to physicians regarding the monitoring and treatment of women with SLE that want to become pregnant.

Key Words. Lupus, Pregnancy, Review

Introduction

Systemic lupus erythematosus (SLE) is a prototypic human autoimmune disease and a disorder of generalized autoimmunity that predominantly affects women during their childbearing years (1,2). The management of pregnant patients with SLE presents a challenge to physicians, because pregnancy and SLE can aggravate each other. However, there is insufficient evidence to support the notion that SLE has a deleterious effect on fertility (3,4). Overall, about 20% of pregnancies in women with SLE end in miscarriage or stillbirth, and the risk of preterm birth has been estimated to be 33% for all lupus pregnancies (5). Furthermore, a severe disease flare may be potentially life threatening, and the drugs used to treat SLE can adversely affect the fetus. Thus, pregnancy is an important clinical setting for disease management in SLE patients, because these patients are at a higher risk for obstetric complications. Advances in the understanding of the lupus-pregnancy interaction have led to the developments of better monitoring methods and treatments for pregnant SLE patients, but no consensus has been reached on the management of pregnancy in SLE patients.

Pre-pregnancy Evaluation

Here, we review pre-pregnancy evaluations and the management of pregnant women with SLE and provide a general guideline to physicians regarding the monitoring and treatment of women with SLE that want to become pregnant.

Pregnancy Management Plan

A pregnant woman with SLE should be cared for by an obstetrician and a rheumatologist (6) (Table 2). During pregnancy, C3 and C4 may rise to supranormal levels, though a flare may occur despite apparently normal levels. However, a fall in C3 or C4 levels by more than 25% may be considered an indicator of disease activity (11). It is recommended that complement and anti-ds DNA antibodies be measured monthly, and that biochemical profile, a full blood count, and urinalysis be conducted routinely during all SLE pregnancies (10). Furthermore,
blood pressure monitoring is important for the detection of early pregnancy-induced hypertension or preeclampsia, and blood pressures should be measured during each visit.

Doppler studies of uterine and umbilical arteries may help predict complications, such as, preeclampsia and fetal distress, and should be performed from 20 weeks, particularly in women with aPL antibodies, an adverse obstetric history, or with a history of renal disease. Furthermore, repeated ultrasound examinations of the fetal heart are needed between 20 and 30 weeks if the mother is anti-Ro and/or anti-La positive to detect CHB (6) (Table 2). The frequency of clinical visits depends on need, but we recommend monthly visits until 28 weeks, fortnightly visits to 36 weeks, followed by weekly visits (10).

**Drugs in Pregnancy**
The medication that any SLE patient is taking during pregnancy should be carefully reviewed. Most information on drug safety in pregnant women resides in case series and case reports, but recently, a consensus document was published based on an extensive literature review of the safety of a number of drugs commonly used in pregnant women with rheumatic diseases, including SLE (12) (Table 3).

### Non-steroidal anti-inflammatory drugs
Non-steroidal anti-inflammatory drugs (NSAIDs) are not teratogenic and they are generally considered safe. NSAIDs can be continued during the first and second trimesters, but they should be avoided during the last weeks of pregnancy. Four consensus documents have been published, all supporting the use of low-dose aspirin in pregnant women with antiphospholipid syndrome (aPL) who are at high risk of adverse pregnancy outcomes (6). The American College of Rheumatology (ACR) and the American College of Obstetricians and Gynecologists (ACOG) recommend low-dose aspirin in women with aPL antibodies and prior adverse obstetric outcome (13). The non-steroidal anti-inflammatory drugs that can be continued during pregnancy are those indicated for maternal use (12).

### Drug constraints during pregnancy and lactation

**Table 1. Pre-pregnancy checklist (Adapted from reference (7))**

<table>
<thead>
<tr>
<th>Age</th>
<th>Any previous pregnancy</th>
<th>Previous pregnancy complications</th>
<th>SLE organ involvement</th>
<th>Degree of irreversible damage</th>
<th>Recent or current SLE activity</th>
<th>Presence of aPL antibodies</th>
<th>Positivity of anti-Ro and/or anti-La antibodies</th>
<th>Current treatment: any forbidden drugs</th>
</tr>
</thead>
</table>

SLE: Systemic lupus erythematosus, aPL: anti-phospholipid

**Table 2. Pregnancy management plan (Adapted from reference (6))**

| Coordinated care by a medical-obstetric team with experience in autoimmune diseases and high-risk pregnancies | Fully equipped neonatal unit | Full autoantibody profile available before pregnancy | Visits more frequent as pregnancy progresses | Blood pressure and urine dipstick on every visit | Uterine artery Doppler study at 20 weeks in patients with aPL antibodies, renal disease, hypertension or history of preeclampsia. Repeat at 24 weeks if abnormal | Umbilical artery Doppler study from 20 weeks, with frequency according to medical and obstetric course, in women with aPL antibodies, renal disease, active disease or previous complicated pregnancy | Uterine artery Doppler study from 20 weeks in women with anti-Ro and/or anti-La antibodies |

**Table 3. Drug constraints during pregnancy and lactation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>NSAIDs</th>
<th>Low dose aspirin</th>
<th>Prednisone</th>
<th>Dexamethasone</th>
<th>Betamethasone</th>
<th>Hydroxychloroquine</th>
<th>Azathioprine</th>
<th>Methotrexate</th>
<th>Cyclophosphamide</th>
<th>Cyclosporin A</th>
<th>Tacrolimus</th>
<th>Mycophenolate</th>
<th>Intravenous immunoglobulin</th>
<th>Anti-TNF</th>
<th>Bisphosphonate</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA risk</td>
<td>B, C</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>D</td>
<td>X</td>
<td>D</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lactation</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Comments</td>
<td>Avoid third trimester use</td>
<td>No consensus on when to stop low dose aspirin before delivery</td>
<td>Indicated for maternal use</td>
<td>Not recommended for routine use in pregnancy</td>
<td>Not recommended for routine use in pregnancy</td>
<td>When indicated, azathioprine can be used during pregnancy</td>
<td>Can be maintained in pregnancy at the lowest effective dose</td>
<td>May be maintained in pregnancy at the lowest possible dose</td>
<td>Insufficient data on breastfeeding</td>
<td></td>
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</tr>
</tbody>
</table>

**NSAIDs:** nonsteroidal anti-inflammatory drugs, **Anti-TNF:** anti-tumor necrosis factor

The United States Food and Drug Administration (FDA) pregnancy risk categories are as follows: A: no risk in controlled clinical studies in humans, B: human data reassuring, and when absent, animal studies show no risk, C: human data lacking, but animals studies indicate risk or have not been done, D: positive evidence of risk, but benefit may outweigh the risk, X: contraindicated during pregnancy.

**Non-steroidal anti-inflammatory drugs**
Non-steroidal anti-inflammatory drugs (NSAIDs) are not teratogenic and they are generally considered safe. NSAIDs can be continued during the first and second trimesters, but they should be avoided during the last weeks of pregnancy.
pregnancy due to the risk of premature closure of the duc-
tus arteriosus. After gestational week 20, all NSAIDs
(except low-dose aspirin, at less than 100 mg/day) can
cause constriction of the ductus arteriosus and impair fetal
function. Furthermore, all NSAIDs, again except low-dose
aspirin, should be withdrawn at gestational week 32.
Breastfeeding immediately before consumption can help to
minimize infant exposure (12).

Corticosteroids
Corticosteroids do not appear to increase the risk of congeni
tal abnormalities noticeably in humans. Non-fluorinated steroids,
such as, prednisone, prednisolone, and methylprednisolone, are
recommended only for maternal indications. They can be used
in SLE pregnancy, but doses of prednisone >20 mg increase
the risk of both pre-eclampsia and of gestational diabetes in
SLE pregnancies. Breastfeeding is allowed with moderate doses
of steroids. However, fluorinated corticosteroids, such as dex-
amethasone and betamethasone, are not metabolized by the pla-
centa, and thus, reach the fetus, and could cause typical steroid
side effects. Accordingly, fluorinated steroids are not recom-
nended for routine use in pregnancy (12).

Hydroxychloroquine
Hydroxychloroquine (HCQ) use has not been shown an in-
crease the risks of congenital malformations. A meta-analysis
concluded that HCQ is not associated with any increased risk
of congenital defects, spontaneous abortion, fetal death,
pre-maturity, or a decrease in the number of live births. HCQ
should be continued during pregnancy when indicated, be-
cause its discontinuation increases disease activity and the
risks of lupus flare and preterm birth. HCQ is also compatible
with breastfeeding (12,13).

Azathioprine
When indicated, azathioprine can be used during pregnancy
at a daily dose not exceeding 2 mg/kg per day. Azathioprine
has a long track record of use in pregnancy and has an accept-
able safety profile (12).

Methotrexate
Methotrexate (MTX) is contraindicated during pregnancy and
must be withdrawn prophylactically 3 months before a plan-
ned pregnancy. Folate supplementation should be continued
throughout pregnancy and during the antenatal period (12).

Cyclophosphamide
Cyclophosphamide (CYC) is a human teratogen, and thus, must
be avoided during pregnancy. Furthermore, attempts at con-
ception should be delayed until 3 months after CYC cessation.
Breastfeeding while on CYC is not recommended (12).

Cyclosporin A
Although cyclosporin A (CsA) has been associated with
growth restriction, it can be maintained during pregnancy at
its lowest effective dose. No consensus has been reached
among experts regarding the use of CsA and nursing (12).

Tacrolimus
Tacrolimus may be maintained during pregnancy at the lowest
possible dose and breastfeeding is possible (12).

Mycophenolate mofetil
Mycophenolate mofetil (MMF) is contraindicated during preg-
nancy and should be stopped at least 6 weeks before
conception. No data exist on excretion into breast milk, and
thus, breastfeeding is not recommended (12).

Intravenous immunoglobulin
Intravenous immunoglobulin can be used in pregnancy and
breastfeeding is allowed (12).

Biological drugs
Etanercept and infliximab should not be continued during preg-
nancy because of a lack of information, and for the same
reason, the effects of these agents on the nursing child are
not known. Thus, breastfeeding is not recommended (12).

Osteoporosis medications
Because of insufficient data, pregnancy should be postponed
for 6 months after the withdrawal of bisphosphonates.
However, the routine use of oral calcium and vitamin D supple-
ments is recommended during pregnancy and lactation (12).

Special Considerations in SLE Pregnancies

Hypertension
Angiotensin converting enzyme inhibitor and angiotensin re-
ceptor blockers should be stopped before conception, because
they may increase the risk of cardiac and brain malformations
(14). Statins also cannot be used during pregnancy, and only
a few hypertensive medications are acceptable during preg-
nancy, such as, alpha methyldopa, hydralazine, and labetolol
(14). Diuretics are not usually used during pregnancy because
they can decrease intravascular volume, but loop diuretics
may be used if needed in lupus nephritis.
Antiphospholipid antibody syndrome

The presence of aPL antibodies increases the risks of maternal complications like thrombosis, pre-eclampsia with hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome, and of fetal complications, such as, miscarriage, prematurity, intrauterine growth restriction, oligohydramnios, placental abruption, and fetal death (15). Low-dose aspirin should be taken by all women with aPL antibodies, if possible, before conception (16).

For women with aPL antibodies on warfarin who want to become pregnant, patients should be switched from warfarin to heparin early enough to ensure that there is no fetal exposure because warfarin is teratogenic, especially during the 6th and 12th gestation weeks (17). Women can stop warfarin and replace it with heparin either prior to attempted conception or as soon as pregnancy is determined.

Consensus recommendations are that SLE women with aPL antibodies and a history of 2 or more early pregnancy losses or 1 or more late pregnancy losses with no prior history of thrombosis receive treatment with a combination of low-dose aspirin and heparin (unfractionated or low-molecular-weight) during pregnancy (18). Low-dose aspirin should be started at around the time of attempted conception and heparin (5,000 ∼ 10,000 units every 12 hours) or low-molecular-weight heparin should be started in prophylactic doses when a viable intrauterine pregnancy is documented and then continued until late in the third trimester (19).

Lupus nephritis and pre-eclampsia

Pregnant women with SLE are at increased risk of pre-eclampsia, and women with a history of kidney disease are at higher risk of developing pregnancy-induced hypertension and of suffering a renal flare (5). Proteinuria and hypertension are common to both conditions, and lupus nephritis and pre-eclampsia can co-exist. However, they may be differentiated using some clinical features. Rising uric acid levels indicate toxemia, whilst the presences of hematuria and/or cellular casts, extrarenal activity, rising anti-DNA antibody levels, and falling complement levels indicate lupus nephritis (20).

Although the usefulness of antiaggregant durgs to prevent pre-eclampsia has been controversial, a recent meta-analysis showed consistent and significant reductions in the risks of pre-eclampsia, pre-term delivery (at < 34 weeks), and of serious adverse outcomes among women on low-dose aspirin (21).

Anti-Ro and/or anti-La antibodies

Neonatal lupus is associated with maternal anti-Ro and anti-La antibodies, and is characterized by a transient skin rash, thrombocytopenia, hepatitis, and/or a CHB (22). Women with anti-Ro and/or anti-La antibodies are at risk of delivering a baby affected by a complete CHB. CHB is caused by the binding of maternal anti-Ro and/or anti-La antibodies to fetal cardiac tissue, which causes transient myocarditis and subsequent fibrosis of the atrioventricular node (23). CHB is the most serious complication and occurs in 2% of the fetuses of women with the anti-Ro antibody, and has a recurrence rate of 16% in subsequent pregnancies (23). Mortality due to CHB is estimated to be 16 ∼ 19% (24). CHB occurs between gestation weeks 16 and 30, and fetal echocardiography should be performed over this period for early detection (25). Fluorinated steroids are effective for fetuses with CHB, and betamethasone is preferred because of the underlying risks posed by dexamethasone on the fetal brain (26). Neonatal lupus rashes manifest as annular inflammatory lesions usually on the face and scalp during the first 2 weeks of life. However, the rash disappears spontaneously within 6 months (10).

Postpartum lupus flare

The postpartum management of women with SLE is important, since lupus can flare during this time (27). Close postpartum monitoring is also needed for pregnancy-induce lupus flare. In particular, close surveillance during the 4 weeks after delivery is warranted, especially in women with recent activity. Patients would be slowly tapered off corticosteroids in the absence of disease activity. The puerperium is also a high-risk period for thrombosis, and if anticoagulation has been required during pregnancy, adequate anticoagulation should be extended for 4 to 6 weeks after delivery.

Conclusion

The pregnancy and postpartum period are associated with elevated risks for mother with SLE and their fetuses. Careful planning and treatment are required to care for women with lupus who become pregnant. Patients should be evaluated before becoming pregnant and must be followed during pregnancy. Pre-pregnancy counseling, an assessment of disease activity, and determinations of the presences of anti-Ro, La and aPL antibodies are recommended. Regular follow-ups by a rheumatologist and an obstetrician with expertise in high-risk pregnancies are mandatory, and postpartum follow-ups should be conducted. We hope that this review helps with the determination of strategies for the monitoring and treatment of women with SLE who want to become pregnant.
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References