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□ REVIEW □

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 lead 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.

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Here, we review pre-pregnancy evaluations and the managements 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.

Pre-pregnancy Evaluation

The management of pregnancy in SLE should start before conception (6,7). SLE patients wanting to become pregnant should be thoroughly evaluated by a rheumatologist (7) (Table 1). Autoantibodies should be available, particularly, anti-phospholipid (aPL) antibodies, anti-cardiolipin (aCL) antibodies, and lupus anticoagulant (LA), anti-Ro and anti-La antibodies because they are associated with specific pregnancy complications, such as, thrombosis, fetal loss, pre-eclampsia, neonatal lupus, and congenital heart block (CHB) (8,9). Furthermore, to minimize the risk of flare during pregnancy, SLE should be inactive for at least 6 months prior to conception (10).

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 safeties of a number of drugs commonly used in pregnant women with rheumatic diseases, including SLE (12) (Table 3).

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

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

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
Fetal echocardiogram from 20th week in women with anti-Ro and/or anti-La antibodies

aPL: anti-phospholipid

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

Table 3. Drug constraints during pregnancy and lactation

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

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

pregnancy due to the risk of premature closure of the ductus 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 congenital 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 dexamethasone and betamethasone, are not metabolized by the placenta, and thus, reach the fetus, and could cause typical steroid side effects. Accordingly, fluorinated steroids are not recommended for routine use in pregnancy (12).

Hydroxychloroquine

Hydroxychloroquine (HCQ) use has not been shown an increase 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, because 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 acceptable safety profile (12).

Methotrexate

Methotrexate (MTX) is contraindicated during pregnancy and must be withdrawn prophylactically 3 months before a planned 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 conception 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 pregnancy 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 pregnancy 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 supplements is recommended during pregnancy and lactation (12).

Special Considerations in SLE Pregnancies

Hypertension

Angiotensin converting enzyme inhibitor and angiotensin receptor 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 pregnancy, 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, olygohyramnios, 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 contoversy, 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 ant-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 underling 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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