Management of SLE During Pregnancy: A Decision Tree

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A. Since SLE most frequently affects women of reproductive age, the rheumatologist and obstetrician will be faced with counseling and management of prospective and existing pregnancies. There are two principal areas of concern. The first is that the clinical and serologic expression of SLE may be altered by the state of pregnancy. The second concern is that the placenta and fetus may become targets of specific attack by maternal autoantibodies, resulting in a generalized failure of the pregnancy (associated with antiphospholipid antibodies) or specific syndromes of passively acquired neonatal lupus (associated with anti-SSA/Ro and anti-SSB/La antibodies).

B. Sterility and fertility rates for women with SLE are comparable to control groups without disease. However, amenorrhea can occur when disease activity is severe. Moreover, menstrual irregularities have been noted in patients receiving glucocorticoids. This is extremely variable among individuals and cannot be predicted for a particular dosage level or preparation of steroids. Additionally, age-dependent premature ovarian failure occurs in patients receiving cyclophosphamide.

C. Particularly for women with SLE, pregnancy should be a planned event, and pre-pregnancy counseling is optimal. Although patients should be reassured that a successful pregnancy is generally achievable, there are situations in which it is ill-advised from a maternal perspective, fetal perspective, or both. The patient in remission for 6 to 12 months with no prior history of renal disease, hypertension, thrombocytopenia, or antiphospholipid antibodies is likely to have the best pregnancy outcome. However, defining remission is not absolute and may differ from one individual to the next. Clearly a woman who requires less than the equivalent of 7 mg prednisone daily (approximates the physiologic production of glucocorticoids), has not had a recent flare of disease, has normal renal function, no proteinuria, normal blood counts, normal blood pressure, no detectable antibodies to dsDNA, and normal levels of complement is an optimal candidate for pregnancy. However, there are women who continue to require 10 to 15 mg of prednisone daily for continued symptoms such as joint swelling, mild pleuropericarditis, or recalcitrant skin lesions, who may fare well during pregnancy or experience only minor exacerbations. There are asymptomatic patients who have persistently elevated titers of antibodies to dsDNA and low levels of complement. Waiting for normalcy might deny the patient a chance to ever become pregnant. Generally patients with milder forms of disease, albeit active, can proceed through a pregnancy without experiencing irreversible organ damage. Even women with more advanced disease such as those with more severe thrombocytopenia (30-60,000 mm3), renal insufficiency (creatinine 1.5 to 2.0), baseline proteinuria between 1-2 grams, while at far greater risk of maternal flare and/or fetal demise, may have a successful pregnancy. Certainly such women need to be counseled about the high likelihood of premature delivery, preeclampsia, and potential need for preterm hospitalization.

D. In anticipation of pregnancy, discontinuation of some medications with substitution of others is required. For example, many patients with SLE take angiotensin-converting enzyme (ACE) inhibitors for control of hypertension; substitution of another drug is urged. Candidate drugs include the obstetrical favorites such as methyldopa or hydralazine, but beta blockers (if Raynaud's phenomenon is not a problem) may be an alternative. There was initial concern over the use of calcium channel blockers, but there seems to be little indication of untoward effects during pregnancy. Women taking warfarin because of a previous venous thrombosis should be switched to subcutaneous unfractionated heparin or low weight molecular heparin prior to conception. Currently, use of the latter is preferred given the improved safety profile. While it is acknowledged that hydroxychloroquine does cross the human placenta thereby exposing the fetus to potential toxicity, a growing experience with these drugs has not borne out the feared risks of fetal ophthalmic injury. The possibility that discontinuation of hydroxychloroquine may trigger a lupus flare seems to outweigh potential risks. Women receiving cyclophosphamide (i.v. or orally) or methotrexate should not become pregnant until after these drugs have been discontinued.

E. For certain patients pregnancy should be delayed and for others aggressively discouraged. Since lupus is a disease characterized by exacerbations and remissions, it is obvious that a patient with active organ disease on

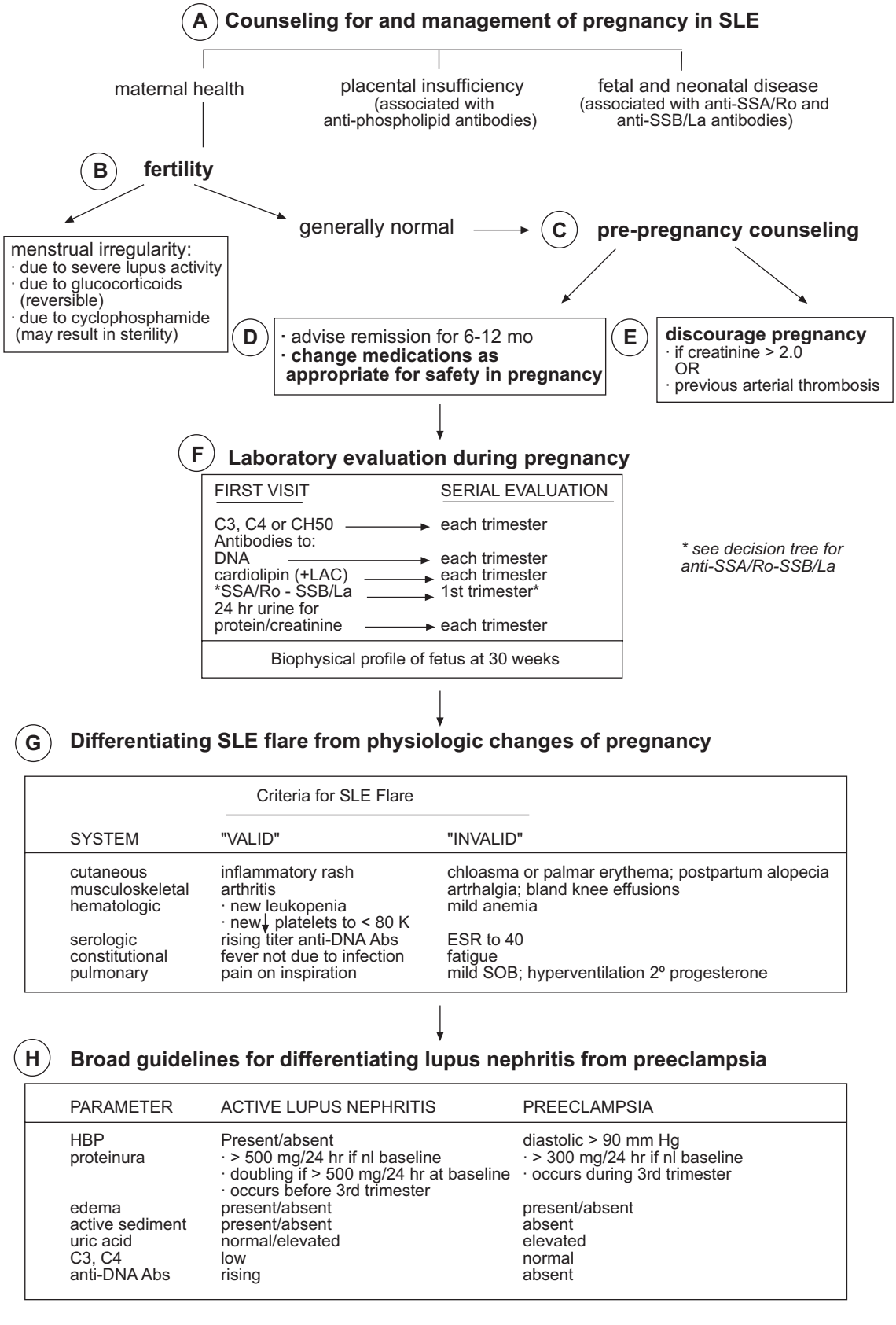
doses of prednisone > 0.5 mg/kg/day should delay pregnancy. Fortunately there are only a few situations in which childbearing should probably not be contemplated at all. For patients with significant renal insufficiency (serum creatinine levels > 2.0) the risk of further renal deterioration may be unacceptably high and fetal outcome is poor. Women with anti-phospholipid antibodies and a previous arterial thrombosis or pulmonary embolus are generally counseled against pregnancy. Despite aggressive treatment of secondary anti-phospholipid syndrome, the risk of recurrent thromboembolism is high, as is the risk of fetal demise.

F. At the first prenatal visit an extensive evaluation should be performed on every patient despite how well the patient may appear. This includes a complete blood count with differential, full electrolyte panel, liver function studies, serum creatinine, albumin, dipstick and microscopic analysis of the urine, 24-hour urinary excretion of protein and creatinine, anti-dsDNA antibodies, anti-cardiolipin antibodies (inclusive of anti-β_2 glycoprotein I antibodies as well), lupus anticoagulant [best measured by a dilute Russell's viper venom time (dRVVT)], C3 and C4, and anti-SSA/Ro-SSB/La antibodies. Many of these tests will provide critical baseline information with which subsequent testing can be compared. Although the level of disease activity ultimately dictates the frequency of blood and urine testing, it is generally recommended that anti-dsDNA, C3, C4, and 24-hr protein be done each trimester. Anti-SSA/Ro-SSB/La antibodies need only be evaluated once.

G. There are conflicting data on whether lupus flares are more common in pregnancy, even in well-controlled studies. One factor may be patient selection, with flare rates being higher in African-American compared to Caucasian patients. A major reason for discrepant results is in the definition of a lupus flare during pregnancy. No currently validated standard disease activity scale considers the normal physiologic changes of pregnancy, but several scales are being modified and validated. Examples of confounders are the increase in glomerular filtration rate, increase in plasma blood volume, leukocytosis and increased erythrocyte sedimentation rate, and palmar erythema. In applying the Systemic Lupus Activity Measure (SLAM) to the pregnant lupus patient, fatigue, alopecia, decreased hematocrit, and ESR may not represent lupus activity. Suggestions for "valid" criteria attributable to a flare are characteristic dermatologic involvement, arthritis, hematuria, fever not secondary to infection, lymphadenopathy, leukopenia, alternative-pathway hypocomplementemia, and rising titers of antibodies to DNA. Careful consideration should be given before a symptom or sign is unambiguously attributed to lupus and treatment instituted. In our experience and others there seems to be a consensus that flares in both the renal and hematologic systems are more common during pregnancy. The timing of flares is variable, with some investigators reporting increased flares in the latter half of pregnancy and early postpartum. There is no proven efficacy in the prophylactic use of prednisone either early in pregnancy or postpartum in a patient not currently on prednisone.

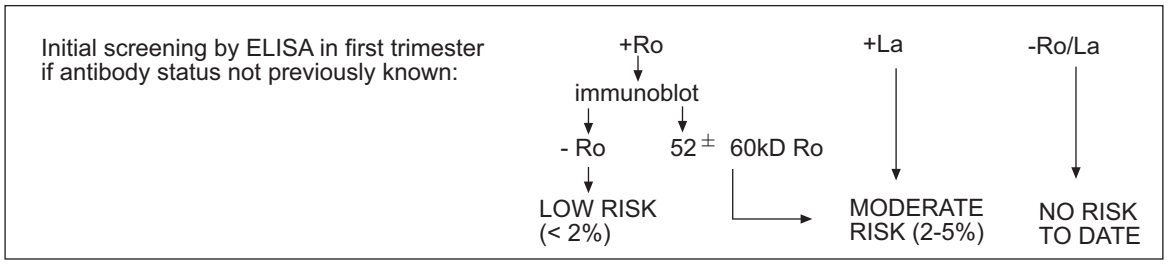
H. In counseling a patient about the maternal risks of a prospective pregnancy, a major issue is the occurrence and/or deterioration of renal disease during pregnancy. The former is less likely to be first manifest during pregnancy in the absence of any prior renal involvement. However, in patients with pre-existing glomerulonephritis, there is frequently an increase in proteinuria. This may be secondary to the normal increase in glomerular filtration rate observed in the second trimester, which in a patient with fixed glomerular lesions may result in protein excretion greater than 300 mg/24 hr. The kidneys are probably the most difficult organ system to unequivocally ascribe to active lupus rather than pregnancy, especially if the patient does have a history of underlying renal disease. Because the risk of bleeding after renal biopsy is greater during pregnancy, there is increased reliance on laboratory parameters. In the complete absence of proteinuria, hematuria solely related to active nephritis (except mesangial) is unlikely. Proteinuria presents the greatest confusion. In the absence of evidence to suggest preeclampsia (see below), the following findings support active lupus nephritis:

1) The baseline 24-hr protein excretion is normal (< 150 mg/24 hr) and the subsequent 24-hr protein exceeds 500 mg/24 hr.
2) The baseline proteinuria is > 500 mg/24 hr and doubles on subsequent testing.
3) Although a normal blood pressure argues against preeclampsia, hypertension can certainly accompany proliferative nephritis.
4) An active urinary sediment (RBC casts and/or WBC casts) is characteristic of the proliferative forms of lupus nephritis; however, an inactive sediment should not necessarily imply pregnancy-induced proteinuria alone since it is well recognized that membranous nephritis is often accompanied by a "bland" sediment.
5) Development of proteinuria before the third trimester.
6) A fall in complement levels (C3, C4, or CH50).
7) A rise in titer of anti-DNA antibodies.
8) Evidence of lupus activity in other organ systems is helpful, but nephritis can exist in isolation.


A Counseling for and management of pregnancy in SLE
maternal health
placental insufficiency (associated with anti-phospholipid antibodies)
fetal and neonatal disease (associated with anti-SSA/Ro and anti-SSB/La antibodies)
B fertility
menstrual irregularity:
· due to severe lupus activity
· due to glucocorticoids (reversible)
· due to cyclophosphamide (may result in sterility)
generally normal
C pre-pregnancy counseling
D
· advise remission for 6-12 mo
· change medications as appropriate for safety in pregnancy
E
discourage pregnancy
· if creatinine > 2.0 OR
· previous arterial thrombosis
F Laboratory evaluation during pregnancy
FIRST VISIT
SERIAL EVALUATION
C3, C4 or CH50 → each trimester
Antibodies to:
DNA → each trimester
cardiolipin (+LAC) → each trimester
SSA/Ro - SSB/La → 1st trimester
24 hr urine for protein/creatinine → each trimester
Biophysical profile of fetus at 30 weeks
* see decision tree for anti-SSA/Ro-SSB/La
G Differentiating SLE flare from physiologic changes of pregnancy
Criteria for SLE Flare
SYSTEM | "VALID" | "INVALID"
cutaneous | inflammatory rash | chloasma or palmar erythema; postpartum alopecia
musculoskeletal | arthritis | artrhalgia; bland knee effusions
hematologic | · new leukopenia · new↓ platelets to < 80 K | mild anemia
serologic | rising titer anti-DNA Abs | ESR to 40
constitutional | fever not due to infection | fatigue
pulmonary | pain on inspiration | mild SOB; hyperventilation 2º progesterone
H Broad guidelines for differentiating lupus nephritis from preeclampsia
PARAMETER | ACTIVE LUPUS NEPHRITIS | PREECLAMPSIA
HBP | Present/absent | diastolic > 90 mm Hg
proteinura | · > 500 mg/24 hr if nl baseline · doubling if > 500 mg/24 hr at baseline · occurs before 3rd trimester | · > 300 mg/24 hr if nl baseline · occurs during 3rd trimester
edema | present/absent | present/absent
active sediment | present/absent | absent
uric acid | normal/elevated | elevated
C3, C4 | low | normal
anti-DNA Abs | rising | absent

DECISION TREE - Managing pregnancy in women at risk for offspring with Neonatal Lupus

Laboratory evaluation of pregnant women with autoimmune disorders



Prophylactic approach

HIGH RISK MOTHERS (15-20%) (previous child with any manifestation of NLS): Fetal echo weekly from 16-34 wk*	LOW RISK MOTHERS: Fetal echo every other week from 16-34 wk	MODERATE RISK MOTHERS: Fetal echocardiogram weekly from 16 - 26 wk, then at wk 28, 30, 32, 34*

*Most important to do echo at 16 - 24 weeks, followed by auscultation at frequent intervals if echo not readily available

If echo indicates prolonged mechanical PR interval or advanced degrees of block, then

Therapeutic approach to CHB diagnosed *in utero*

SITUATION	TREATMENT
1. Degree of block at presentation	
• 3rdº (> 2 wk from detection)	• Evaluation by serial echocardiograms and obstetrical sonograms is done; no therapy is initiated.
• 3rdº (< 2 wk from detection)	• 4 mg p.o. dexamethasone daily for 6 wk. If no change, taper. If reversal to 2ndº or better, continue until delivery, then taper.
• Alternating 2ndº/3rdº	• 4 mg p.o. dex daily for 6 wk. If progression to 3rdº, taper. If reversal to 2ndº or better, continue until delivery, then taper.
• 2ndº	
• Prolonged mechanical PR Interval (1stº)	• 4 mg p.o. dex daily until delivery, then taper, unless progression to 3rdº for 6 wk, then taper
2. Block associated with signs of myocarditis, CHF and/or hydropic changes	• 4 mg p.o. dex daily until improvement, then taper.
3. Severely hydropic fetus	• 4 mg p.o. dex daily plus apheresis as a last resort to rapidly remove maternal antibodies, or deliver if lungs are mature.

At birth: obtain EKG, CBC, alkaline phosphatase and transaminases on neonate.
Caution mother and child to avoid sun exposure.

Counsel mother about recurrence rates in subsequent pregnancies. EKG in any siblings.

9) The presence of complement activation products such as C3a, Ba or Bb are supportive of lupus nephritis but may be impractical to obtain in a commercial laboratory and in rare circumstances are also elevated in preeclampsia.

Initiation of the equivalent of 1 mg/kg per day of prednisone in the presence of a significant rise in proteinuria and an active sediment with or without falling complement values and rising DNA antibodies is justified. Proteinuria, even in the absence of an active sediment, may warrant a trial of steroids. Persistent proteinuria > 3 grams/24 hr does not generally predict a good outcome for the mother or fetus. In the absence of any response within two weeks, a reassessment of the situation is warranted with consideration given to the addition of cytotoxic agents and early termination, especially in the setting of deteriorating renal function and an active sediment.

Superimposed preeclampsia is especially difficult to diagnose in the hypertensive woman with proteinuria at the onset of pregnancy. A rising serum uric acid and decreasing creatinine clearance in the absence of an active sediment would suggest preeclampsia rather than SLE. In a patient with no prior history of renal involvement and normal baseline urinary parameters, preeclampsia is strongly supported by the onset of proteinuria in the third trimester, new hypertension, inactive sediment, absence of anti-DNA antibodies, normal complement levels, and no other evidence of active lupus. In the final analysis, the development of preeclampsia in an SLE patient without extrarenal evidence of disease flare is a major diagnostic dilemma in which no single clinical or serological test is definitive. It is readily acknowledged that in some patients the two conditions coexist.

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