Updates on Lupus and Pregnancy

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Abstract
This review focuses on events subsequent to planning a pregnancy and addresses three components of concern for women with systemic lupus erythematosus: maternal, placental, and fetal. Flare rates are generally low for patients who are clinically stable at conception. For patients who have never had renal disease, there is no firm evidence that they will develop active renal disease simply due to being pregnant. For patients who begin pregnancy with an abnormal creatinine (> 2 mg/dl is ill advised), risks include hypertension, preeclampsia, high rate of fetal loss, and possible further deterioration of renal function. Discontinuation of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and mycophenolate is mandatory. Elevated levels of sVEGF-1 may be a harbinger of preeclampsia. For patients with anti-phospholipid antibodies detected in the first trimester of pregnancy, the lupus anticoagulant per se may be the strongest predictor of pregnancy complications. For women with anti-SSA/Ro antibodies the risk of having a child with congenital heart block is 2% which rises to a recurrence rate of 18%. Information on current approaches to prevention and treatment of heart complications of neonatal lupus is provided.

Given the extraordinary dominance of females as the risk group for systemic lupus erythematosus (SLE) and the peak incidence of disease onset during the reproductive years, counsel regarding pregnancy is surely inevitable. Further supporting the importance of such counsel is that fertility is generally normal in these women, unless there has been prolonged exposure to intravenous cyclophosphamide. Accordingly, dialogue regarding pregnancy is best initiated in a planning phase to assure optimal timing (avoidance during flares) and adjustment of medications. This review will focus on events subsequent to planning and address the triple threats of pregnancy, which include maternal, placental, and fetal components. The goal is not to present an exhaustive review but rather to provide updates on current thinking, which in some areas has not changed in a decade, and data from ongoing clinical studies and trials.

The Maternal Component
With regard to the maternal component, the patient’s main concern is whether or not her SLE will flare. As physicians caring for these women, we accept that all flares are not equal, and the questions patients are more likely to be asking us are whether the flare would be serious enough to require medications, to negatively impact activities of daily living, to require hospitalization, or to permanently damage the kidneys. In contrast to the “rule of remission” during pregnancies in women with rheumatoid arthritis, the influence of pregnancy on disease activity in women with SLE is variable. Since SLE is a chronic disease punctuated by episodes of acute illness and spontaneous remission, the attribution of a disease flare to pregnancy may not be straightforward. Thus, it is important to consider physiologic and immunologic adaptations, as they may account for or influence a patient’s signs or symptoms.

Current definitions of flare are imprecise, and accepted instruments used to measure disease activity, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) or Systemic Lupus Activity Measurement (SLAM), do not account for the physiologic adaptations of pregnancy and, as well, have not been validated for pregnant lupus patients. Suggestions for “valid” criteria attributable to
a flare are characteristic dermatologic involvement, arthritis, hematuria, fever not secondary to infection, pain on inspiration, lymphadenopathy, leukopenia, thrombocytopenia less than 80,000/mm³, falling complement levels, and rising titers of antibodies to DNA. In contrast, “invalid” markers of disease activity include alopecia, facial or palmar blush, arthralgia, musculoskeletal aching, mild anemia, fatigue, mild shortness of breath, and hyperventilation, which may reflect high progesterone levels. One of the activity instruments being currently utilized in clinical studies is the SLEPDAI (“P” stands for pregnancy), in which the managing physician is instructed to score each domain on SLEPDAI in the context of a potential influence on pregnancy. Flares are divided into mild-moderate and severe and follow the same guidelines as the SELENA-SLEDAI flare index.¹ In 1997, Petri and colleagues compared organ system involvement in pregnant and nonpregnant SLE patients, and the only two systems that emerged as more significant in pregnancy were renal and hematologic.² These observations have withstood the test of time.

For patients who have never had renal disease, it is unlikely they will develop active renal disease simply due to being pregnant. Nevertheless, constant vigilance is appropriate with at least a protein-creatinine ratio and microscopic analysis of urine done each trimester. The same management holds true for those patients who have had lupus nephritis but have experienced full remission and begin pregnancy with a normal level of creatinine and no proteinuria. It is expected that monthly obstetrical visits during the first and second trimesters and even more frequently during the third trimester should reveal any abnormalities, since dipstick of the urine is part of routine care. For patients who begin pregnancy with an abnormal creatinine (greater than 2 mg/dl is usually ill advised), there are clear risks, and these need to be fully disclosed to patients. Risks include hypertension, preeclampsia, high rate of fetal loss, and possible further deterioration of renal function. On a practical level, there are adjustments that must be made during pregnancy, and discontinuation of mycophenolate mofetil is one of them. If there remains a concern regarding high risk of renal flare based on an individual patient, then it may be prudent to switch to azathioprine. It is also a bit of a diagnostic dilemma with regard to angiotensin converting enzyme inhibitors and angiotensin receptor blockers, because these medications should also be discontinued. However, doing so may result in worsening of proteinuria and hypertension.

Over the last five years, Jane Salmon, M.D., and her colleagues have been enrolling patients into the NIH (National Institutes of Health) study “Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Syndrome and Systemic Lupus Erythematosus (PROMISSE).” This multicenter observational study was initially launched to identify markers of poor pregnancy outcome in patients with antiphospholipid antibodies (aPL) alone and was expanded to include patients with both aPL and SLE, as well as SLE alone. The first results of this prospective study were presented in abstract form at the national meeting of the American College of Rheumatology in the fall of 2008.³ Nearly 200 SLE patients were evaluated over the course of pregnancy and 3 months postpartum. Importantly, patients had to be stable or only mildly active at entry. Specifically, the patients had to be on less than 20 mg prednisone and excerting less than 1 gram of proteinuria per 24 hours. However, previous renal disease was not an exclusion criterion and approximately one-third of patients had past renal involvement, and 50% had anti-dsDNA antibodies at 12 weeks of gestation. Consistent with the prevailing notion that patients in remission tend to remain in remission, flare rates were very low in this cohort. Specifically, 6% had mild flares in the mid-second trimester, 5% had mild flares in the third trimester, and 8% had mild flares postpartum. In general, these flares were restricted to the musculoskeletal or cutaneous systems. With regard to severe flares, there were none in the second trimester, 1% in the third trimester, and 2% in the postpartum period. Only one patient developed nephritis, which occurred postpartum. However, despite the overall good health of these women, approximately 15% developed preeclampsia (not obviously associated with aPL), and with a similar percent, the pregnancy ended in a preterm delivery. The investigators concluded that, based on these first results, mild to moderate and severe flares were extremely infrequent in pregnant SLE patients who are clinically stable at conception, even in the presence of anti-dsDNA antibodies and a past history of renal disease, or either alone.

The issue of preeclampsia is important, and differentiating it from lupus nephritis is probably the most common reason rheumatologists are called to consult on a patient. Preeclampsia is defined as hypertension (systolic: BP 140 mm Hg or diastolic: BP 90 mm Hg) on two occasions, 4 hours apart plus at least one of the following: 1. proteinuria, if baseline is less than 100 mg/24 hr, then 300 mg/24 hr, or dipstick results of 2+ (100 mg/dl) are recorded at least 4 hours apart; 2. no proteinuria, if baseline is less than 100 mg/24 hr, then 300 mg/24 hr, or dipstick results of 2+ (100 mg/dl) are recorded at least 4 hours apart; 3. platelet count is less than 100,000 cells/mm³; or 3. pulmonary edema is present. Severe preeclampsia includes the HELLP syndrome, which is a microangiopathy comprised of hemolysis (LDH > 600 IU/L), elevated liver enzymes (AST more than 70 IU/L), and low platelets (less than 100,000 cells/mm³).

During pregnancy, the “proposed increment in proteinuria” may inaccurately assign [SLE renal] activity when there is none. Therefore, it may be more judicious to consider a doubling of proteinuria if the baseline is greater than 500 mg/24 hr. While a normal blood pressure argues against preeclampsia, an inactive sediment should not necessarily imply a pregnancy-related phenomenon, since it is well recognized that membranous nephritis is often accompanied by a “bland” sediment. The presence of edema is not helpful, since it is a physiologic finding present in many normal
pregnant women. Proteinuria developing before the third trimester often suggests underlying renal disease. Superimposed preeclampsia is especially difficult to diagnose in the hypertensive woman with proteinuria at the onset of pregnancy. A rising serum uric acid...in the absence of an active sediment would suggest preeclampsia rather than SLE. Preeclampsia can also be associated with elevations of a variety of complement split products (Ba, C3a, C4d, SC5b-9), indicating activation of both the classical and alternative pathways. However, the CH50 levels tend to be normal.... 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. In the absence of a renal biopsy, physician judgment prevails and the final diagnosis may require follow-up [before confident attribution to SLE or preeclampsia can be made].

Notable proteinuria associated with preeclampsia can persist, albeit generally decreasing, for several months postpartum.

With regard to the pathogenesis of preeclampsia, angiogenic dysregulation has been a recent focus. Normal placental development requires the expression of angiogenic growth factors, such as vascular endothelial growth factor (VEGF), which promotes placental development through the interaction with VEGF receptor-1 (also known as FLT-1). Excess soluble VEGFR-1 (a product of alternative splicing of VEGFR-1 also referred to as sVEGFR-1 or sFLT-1) inhibits placental cytotrophoblast differentiation and invasion and contributes to the abnormal placentation associated with preeclampsia. In the general population, Levine and coworkers have reported evidence of angiogenic dysregulation in preeclampsia. There was a significantly increased level of sVEGF-1 in patients with preeclampsia compared to controls. Petri and associates published similar findings in patients with SLE and associated preeclampsia. Salmon and associates reported that, based on early results of the PROMISSE study, the rate of increase of sVEGF-1 during pregnancy was significantly higher in SLE and aPL patients who developed preeclampsia. Whether markers of angiogenic dysregulation prove to be an important predictor of preeclampsia is not firmly established but should be answerable with the PROMISSE study.

The Placental Component

In addition to maternal considerations, another concern is that the placenta and fetus may become targets of specific attack by maternal autoantibodies, resulting in a generalized failure of the pregnancy or specific syndromes of passively acquired autoimmunity, such as neonatal lupus. aPL antibodies are associated with fetal or embryonic death in 16% to 38% of pregnancies, growth restriction in 15% to 30% of pregnancies, and preeclampsia in 18% of pregnancies. Once documentation of aPL has been made in a woman with recurrent fetal loss (excluding anatomic, chromosomal, and hormonal abnormalities), there are several rational protocols to consider. To date there is no single best recommendation. It has been suggested that healthy women or those with SLE and two or fewer losses before 10 weeks and no fetal loss undergo close maternal-fetal monitoring. Although low dose aspirin (81 mg daily) may not be effective, it may be chosen for some patients with aPL. Aspirin should be initiated either during preconception or at the time of a positive pregnancy test. Heparin regimens are recommended for women with clear prior aPL related events, with low molecular weight preparations preferred. Heparin therapy is usually initiated at the time of detection of fetal heart activity, which is generally at 6 weeks of gestation. Prophylaxis of heparin-induced osteoporosis with supplementation of calcium and vitamin D should be initiated in all patients on heparin.

Perhaps some of the most clinically relevant advances in the approach to a patient with aPL are the recent findings, again, obtained from the PROMISSE study. Salmon and colleagues reported on the results of 65 patients with aPL in the absence of SLE and 36 patients with aPL in association with SLE. Overall, there was a poor pregnancy outcome in 20% of patients. Of 47 patients who had no evidence of a lupus anticoagulant, none had a poor outcome, in contrast to 18 (41%) of 44 patients who did. Interestingly, many patients with high titer anti-cardiolipin antibodies or anti-β2-glycoprotein I antibodies, in the absence of a lupus anticoagulant, had uncomplicated pregnancies. Moreover, treatment with heparin, glucocorticoids, or hydroxychloroquine was not a significant predictor of pregnancy outcome in multivariate analyses. The conclusion of these findings is that for patients with aPL detected in the first trimester of pregnancy, the lupus anticoagulant is the strongest predictor of serious pregnancy complications. Identification of patients at high risk will be highly informative in designing trials to prevent aPL-associated maternal and fetal morbidity.

The Fetal Component

Neonatal lupus comprises several fetal and neonatal manifestations that share in common the in utero exposure to maternal anti-SSA/Ro antibodies (with or without anti-SSB/La antibodies). The most common manifestations are cutaneous and cardiac, the former resembling the lesions observed in SLE, which are likely responsible for the name given to this disease. Tissue injury in the fetus is presumed to be dependent on the FcRn-mediated transplacental passage of maternal IgG autoantibodies. Disease in the offspring parallels the presence of maternal antibodies in the fetal and neonatal circulation and disappears, except for cardiac injury, with the clearance of these antibodies by the eighth month of postnatal life. The transient nature of the rash reflects the effect of passively acquired autoantibodies on an organ system with the capacity of continual regeneration. In contrast, these regenerative processes apparently do not occur in cardiac tissue; third-degree block is irreversible to date. The signature cardiac lesion is atrioventricular block [congenital heart block (CHB)], but in 15% to 20% of cases there is an associated, frequently fatal, cardiomyopathy.
Most affected children require permanent pacemakers before adulthood, 50% of which are placed during the neonatal period. Several clinical facts are important for the counseling of women with anti-SSA/Ro antibodies. Disease in the mother does not appear to influence the development of CHB in an offspring. The risk of a primigravid female or one who has had only healthy children is 2%, which may nudge up to 3% to 5% if there are associated anti-SSB/La antibodies. The recurrence rate is approximately 18%. The maternal heart is not affected. The diagnosis of CHB is generally made between 18 to 24 weeks of gestation. What is most disturbing is that, based on serial echocardiograms, the fetus can progress from normal sinus rhythm (NSR) to complete block in 7 days. The histologic signature of disease is fibrotic replacement of the atrioventricular node. The spectrum of block can cover first to third degree but most commonly is advanced. The significance of first-degree block is not firmly established (see below).

Given the rarity of neonatal lupus, the NIH, in conjunction with New York University School of Medicine, established the Research Registry for Neonatal Lupus in 1994. To date there are 417 families enrolled. Of the 454 mothers with neonatal lupus, 263 have CHB, 141 rash, 36 CHB and rash, six isolated cardiomyopathy, and eight hepatic or hematologic manifestations, or both. This large data set facilitates basic and clinical advances. Based on this considerable data set, it is clear that cardiac manifestations of neonatal lupus are not related to birth order. For 138 families with two children, 11 had both children affected with CHB; in 69 families, the second child had CHB, and, in 58, the first child had CHB. There is one family in which the fifth of six children had CHB. A child with rash can also follow a child with CHB and vice versa. The recurrence of CHB in a subsequent pregnancy appears to be unaffected by maternal health and antibody status, by the use of steroids or by fetal gender or death of the previous child with CHB.

Since fetuses presenting with third-degree block may not benefit from treatment, the critical times to intervene would be: 1. when the PR interval is prolonged but atrial signals continue to reach the ventricles (first- or second-degree block) or 2. when signs of myocardial dysfunction alone are present. From the clinical perspective, there is a clear need to identify an early marker of CHB. Accordingly, a US-based observational study [PR Interval and Dexamethasone Evaluation (PRIDE)] of pregnant women known to have anti-SSA/Ro antibodies was initiated, in which echocardiograms were performed serially, beginning at 16 weeks of gestation. The primary outcome measure was the mechanical PR interval, defined using the gated-pulsed Doppler technique as the time interval from the onset of the mitral A wave (atrial systole) to the onset of the aortic pulsed Doppler tracing (ventricular systole) within the same left ventricular cardiac cycle. Secondary outcomes included evaluation of myocardial function. The goal was to determine the earliest non-invasive echocardiographic marker of injury. In the study, 118 pregnant women with anti-SSA/Ro antibodies were enrolled, with 98 completing an evaluable course. The protocol entailed fetal echocardiograms weekly from 16 to 26 weeks of gestation and biweekly from 26 to 34 weeks. PR intervals greater than 150 msec (mean +3 SD) were considered abnormally prolonged, consistent with first-degree block; 92 fetuses had normal PR intervals throughout the study. Neonatal lupus developed in 10 cases, four of which were rash only. Three fetuses had third-degree block, none of whom had a preceding abnormal PR interval, albeit, in two, more than 1 week elapsed between echocardiographic evaluations. Tricuspid regurgitation preceded complete block in one fetus, and an atrial echodensity preceded the block in a second fetus. Three fetuses had a PR interval greater than 150 msec. Two, each detected before 21 weeks, reversed within 1 week after institution of 4 mg of dexamethasone. Whether dexamethasone was curative or incidental could not be assigned. A third case developed first-degree block at birth (32 weeks gestation) as demonstrated by ECG after normal PR intervals in utero; the block persists at age 3 years. Importantly, no conduction abnormalities developed after a normal EKG at birth. Heart block (combining all degrees) occurred in 3 (19%) of 16 pregnancies in mothers with a previous CHB child and 3 (4%) of 74 with no previously affected children. The conclusion of this study was that first-degree block is no more common than third-degree block but, unlike the latter, may be reversible. Advanced block and cardiomyopathy can occur within 1 week of a normal echocardiogram without initial first-degree block. Echodensities and tricuspid regurgitation merit attention as early signs of injury.

Another aim of the PRIDE study was to evaluate the efficacy of dexamethasone in anti-Ro-exposed fetuses who were newly diagnosed with CHB. This was a multicenter open label study involving 30 pregnancies treated with dexamethasone (22 third-degree, 6 second-degree, 2 first-degree) and 10 untreated (9 third-degree, 1 first-degree). Initial median ventricular rates, age at diagnosis, and degree of cardiac dysfunction were similar between groups. Six deaths occurred in the dexamethasone group. There was no reversal of third-degree block with therapy or spontaneously. In fetuses treated with dexamethasone, one of six with second-degree block progressed to third degree, and three remained in second degree (one paced, two progressed to third degree); two reverted to NSR (one progressed to second). Dexamethasone reversed both fetuses with first degree to NSR by 7 days, with no regression upon discontinuation. Absent dexamethasone, the one first-degree fetus, detected at 38 weeks, had NSR at birth (overall stability or improvement 4/8 treated vs 1/1 untreated). Median gestational birth age was 37 weeks versus 38 weeks, dexamethasone versus non-dexamethasone, p = 0.019. Those born premature and small for gestational age were restricted to the treated group. Pacemaker use and growth parameters at birth and 1 year were similar between groups. These data confirm the irreversibility of third-degree block and progression of
second- to third-degree, despite intervention. A potential benefit of dexamethasone in reversing first- or second-degree was supported in rare cases, but should be weighed against potential steroid side effects, such as growth restriction.

The morbidity and mortality of third-degree block suggests the need for development of a new prophylactic therapy, other than dexamethasone, to be given early in pregnancy before the onset of disease, perhaps targeted to the highest risk pregnancies, such as those with a prior affected fetus. Therapy should be targeted either to eliminating the “necessary” factor (no antibody, no disease) or modifying the inflammatory component before it provokes an irreversible scarring phenotype of the fibroblast. IgG pooled from the plasma of healthy donors (immune globulin therapy, also known as IVIG) is a promising agent that might have an effect at several levels of the proposed pathologic cascade. In a study comprised of eight pregnancies in mothers with anti-SSA/Ro antibodies and a previous child with CHB, treatment with 1 gm/kg of IVIG at the 14th and 18th week of gestation prevented CHB in seven cases. 17 IVIG may be particularly effective in prevention of the passively acquired autoimmune disease of CHB. The rationale considers several potential mechanisms, the first two relate to lowering or even eliminating maternal antibody in the fetal circulation (maternal perspective): increased catabolism of maternal antibody and decreased placental transport of maternal antibody. By decreasing antibody levels, there would be less antibody available to bind apoptotic cardiocytes. Thus, the initial cascade to injury might be abrogated. The third consideration is an effect of IVIG transported into the fetal circulation where it might act to upregulate surface expression of the inhibitory FcγRIIIB receptor on fetal macrophages, thereby decreasing secretion of TNFα and exaggerated TGFβ (fetal perspective). Highly speculative would be an anti-apoptotic effect of IVIG, which would certainly be relevant to the pathogenesis of CHB, where we have accumulating evidence that apoptosis of cardiocytes provides an essential link between antibody and fibrosis. Perhaps an effect amplifying the hypothesized mechanisms proposed is the influence of FcγR polymorphisms on the response to IVIG therapy. The PITCH (Preventive IVIG Therapy for Congenital Heart Block) study has recently completed enrollment [http://www.ClinicalTrials.gov (identifier No. NCT00460928)] in an open label study of 19 patients who received IVIG (400 mg/kg IVIG every 3 weeks X 5) from 12 to 24 weeks gestational age. These results and those of a parallel study completed in Europe should be available in the Fall of 2009.

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References