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The Hopins Lupus Pregnancy Center: Ten Key Issues in Management

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Introduction

There is no consensus on the management of SLE, much less pregnancy in SLE patients. However, several key issues in the management of SLE in pregnancy are commonly faced by rheumatologists, nephrologists, and obstetricians. These include the treatment of SLE activity in pregnancy, the ascertainment of lupus nephritis, treatment of antiphospholipid antibodies, treatment of hypertension, and laboratory monitoring. These key issues will be examined in this chapter.

Key Issue #1: Pregnancies in SLE Should be Planned: The Role of Contraception

In the last 21 years at the Hopkins Lupus Center, only a minority of pregnancies are planned. This means that all too often, the patient has active lupus at the time of conception or is on "forbidden" medications. Ideally, SLE should be under good control, on allowed medications, at the time of conception. This means that many women will need to use contraception during periods of moderate to highly active lupus. The following options are available.

Oral Contraceptives

Oral contraceptives are the preferred means of contraception in the general female population. For many years, however, they were forbidden in SLE. This concern was based on studies that suggested an increase in SLE after starting oral contraceptives [1] and an increase in flares, especially renal flares, in patients with established lupus [2]. A further concern was that up to 50% of patients with SLE may have antiphospholipid antibodies; the use of oral contraceptives in a hypercoagulable patient might be the "second hit" leading to thrombosis.

There is an additional need for oral contraceptives beyond contraception in SLE patients [3]. Oral contraceptives are important in the management of endometriosis and ovarian cysts. Ovarian cysts are more common in SLE than in the general female population [4]. Oral contraceptives may help corticosteroids-induced osteoporosis [5]. Oral contraceptives can reduce cyclic activity in SLE.

The Safety of Estrogen in Lupus Erythematosus: National Assessment (SELENA) trial addressed this controversy. Premenopausal SLE women with inactive or stable active lupus

were randomized to a low-estrogen oral contraceptive or to placebo for one year. Women with moderate anticardiolipin or the lupus anticoagulant were excluded. Surprisingly, there was no increase in severe flares – or any flares – in the oral contraceptive arm. In particular, there were more lupus nephritis flares in the placebo arm!

Certainly, the SELENA trial is not blanket approval to use oral contraceptives in all SLE women. A woman with unstable lupus, hypercoagulability due to antiphospholipid antibodies or to nephrotic syndrome or past history of thrombosis, should NOT be given oral contraceptives.

Depo-progesterone

During the decades in which oral contraceptives were forbidden, gynecologists and rheumatologists gained experience in using progesterone-only contraceptives in SLE patients. In murine models, progesterone has no adverse effect on SLE activity [6]. Oral progestin, though, is often unacceptable to women, because of breakthrough bleeding. Depo-progesterone offers convenience, with the need of only quarterly injections.

However, the Food and Drug Administration has advised that the use of depo-progesterone be limited to two years, because of an increased risk of osteoporosis with long-term use. This has led to some consternation in SLE, in which corticosteroid-induced osteoporosis is so prevalent. In women with SLE who have found that deop-progesterone is their preferred method of contraception, bone density scans can be done yearly after two years to monitor for Osteopenia, and compliance with vitamin D and calcium supplementation emphasized.

Intrauterine Device (IUD)

Because older generations of IUD carried an increased risk of infection, experience with IUDs in women with SLE have been limited. With today's IUDs, a woman with SLE who has a single partner and who is not on immunosuppressive drugs other than low dose prednisone, is considered an appropriate candidate. However, we did have a recent case of severe SLE flare soon after IUD injection, that did not remit until the IUD was removed.

Key Issue #2. SLE is Genetic: Will the Children Develop Lupus?

Murine lupus is a genetic disease – but single mutations that have been key in murine lupus, such as fas, have not been important in human SLE. In many murine SLE models, and in human SLE, the disease is polygenic, with as many as 100 different genes playing a role [7]. It is highly likely, however, that a genetic predisposition is not sufficient to develop human SLE. Environmental precipitants include ultraviolet light, infections such as Epstein Barr virus [8], smoking [9], silica, and mercury.

However, the question of whether a child will develop SLE is important to the woman with lupus and to her partner. We believe the best estimate is that 2% of children will develop SLE. By the time they reach adulthood, we expect that not only will there be more effective treatments for SLE, but hopefully "vaccines" to prevent the onset of clinical SLE.

Key Issue #3. What SLE Medicines are Allowed in Pregnancy?

In SLE, control of the disease is mandatory if pregnancy is to be successful. Therefore, we do not ask for perfect safety of medications, but acceptable safety. Excellent reviews of medications in pregnancy are available [10, 11].

Corticosteroids

Prednisone is largely metabolized by the placenta, such that fetal exposure is small. However, doses of prednisone greater than or equal to 20 mg increase the risk of both pre-eclampsia and of gestational diabetes in SLE pregnancy. Thus, there is a strong rationale to keep the prednisone dose below 20 mg.

Moderate to severe SLE flares in pregnancy are likely to require an increase in corticosteroid dosing, at least temporarily. Intravenous methylprednisolone, 1000 mg daily for three days, given over 90 minutes, can help to achieve quick control of a SLE flare, avoiding the need for a high daily maintenance dose. However, some fetal exposure can be expected with higher doses of corticosteroids.

Fetal exposure to corticosteroids may not be completely benign. Later cognitive impairment has been found in premature infants given corticosteroids [12]. This must be balanced against the severe risks experienced by very preterm babies.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

It is well know that NSAIDs should be avoided during the second and third trimesters because of their effect on the ductus arteriosus. NSAIDs can rarely have a deleterious effect on fertility. Only recently was it learned, however, that NSAIDs must be avoided even in the first trimester [13].

Hydroxychloroquine

Initially, there was concern, because of case reports of getal malformations in pregnancies with chloroquine exposure [10]. Both chloroquine and hydroxychloroquine cross the placenta and both are also present in breast milk. The credit for the acceptance of hydroxychloroquine use in pregnancy should be given to Ann Parke [14, 15]. Hydroxychloroquine should be continued during pregnancy, because cessation of hydroxychloroquine leads to increased disease activity, lupus flares, and preterm birth [16].

Azathioprine

Azathioprine has a long track record of use in pregnancy, with an acceptable safety profile [10]. However, there have been rare reports of neonatal immunosuppression.

Mycophenolate mofetil

Mycophenolate mofetil has been associated with rare fetal malformations of the corpus callosum and digits [17]. Currently it is advisable to switch to azathioprine before conception.

Cyclophosphamide

Cyclophosphamide must be avoided during the first and early second trimesters. However, we are now convinced that it should be avoided, even in the third trimester. When we were forced to use it in third trimester in several patients with severe lupus nephritis not responding to high dose corticosteroids and other immunosuppressive drugs, it was followed by intrauterine fetal demise [18].

Cyclosporine

Although cyclosporine has been associated with growth restriction, this may reflect the underlying maternal diseases for which it was prescribed. We have used it, in combination with azathioprine, for lupus nephritis activity in pregnancy.

Key Issue #4. Can We Predict Preterm Birth?

Pregnancy loss gets the most attention, but it is actually preterm birth which is the most common complication of lupus pregnancy. The causes of preterm birth include pre-eclampsia, placental failure, and preterm premature rupture of membranes. Predicting preterm birth could target these pregnancies for high risk obstetric care.

The Hopkins Lupus Center database has identified a combination of two factors: high clinical activity and serologic activity as the best way to predict preterm birth [19]. High clinical activity is defined on a physician's global assessment of disease activity as "2" or higher on a 0 to 3 visual analog scale. This would be considered "moderate" clinical activity. Serologic activity is defined as elevated anti-dsDNA, low C3, or low C4.

Key Issue #5. Are Flares More Common in Lupus Pregnancy?

The hormonal and cytokine changes in normal pregnancy are complex enough – but, in SLE pregnancy, the changes are different! Doria and colleagues [20] found that SLE pregnancies lack the normal increase in estrogen and IL-6, and have higher levels of IL-10 than normal pregnancies.

We found that lupus flares are more common in pregnancy [21] as have others [22]. Other groups, especially when using a matched case-control design, have found no difference [23]. We believe that there are differences based on organ systems. For example, arthritis flares are less common during pregnancy, while renal and hematologic flares are more common. Thus, selection of pregnant patients unlikely to be at risk for SLE flares (i.e., Caucasian women with normal serologies and on no prednisone) may explain the discrepant results.

Key Issue #6. How Can Hypertension Be Treated During Pregnancy?

Rheumatologists have now accepted the "renal sparing" approach of ACE-inhibitors and/or angiotensin receptor blockers, long appreciated by nephrologists. Unfortunately, the rules have changed in terms of using ACE-inhibitors and angiotensin receptor blockers during pregnancy. Before, they were stopped in the first trimester, when pregnancy was first recognized, to avoid fetal renal agenesis. However, it is now necessary to stop them before conception, because of new information on an increase in cardiac and brain malformations [24]. Stopping the "renal sparing" approach also means stopping statins, which cannot be used during pregnancy.

Stopping ACE-inhibitors and angiotensin receptor blockers means that the proteinuria is likely to double, and that hypertension is likely to worsen. Neither result is desirable, but currently there is no alternative. Luckily, blood pressure tends to go down in the first and second trimesters of pregnancy. If a patient is chronically on a thiazide diuretic, we continue it. We try to respect the obstetrician's view that we should not add loop diuretics that might lead to a reduction in the intravascular volume, with detrimental consequences to placental blood flow.

Ultimately, our goal in the non-pregnant patient to strictly control hypertension (aiming for below 120/80) must compromise with the obstetrician's goal to maintain placental blood flow. Thus, the usual goal in pregnancy is to maintain the blood pressure below 140/90, to protect the mother.

Very few hypertensive medications are considered acceptable during pregnancy. Some of those that are acceptable are almost never used in the routine management of hypertension, because of inferior efficacy to other drugs. Thus, the rheumatologist must learn how to dose alpha methyldopa and hydralazine! Usually we find it necessary to add labetolol, which has an excellent safety record in pregnancy.

Key Issue #7. How Can Lupus Nephritis Be Diagnosed in Pregnancy?

Lupus nephritis and pre-eclampsia can co-exist. The treatment of pre-eclampsia is to deliver the placenta and fetus. Delaying the appropriate treatment of severe lupus nephritis until after delivery can have disastrous consequences for the mother. However, both patient and physician want delivery of a viable infant, which may require delaying the most efficacious treatment for a few days to weeks.

Often the diagnosis of lupus nephritis is simple, because in addition to urine protein and active sediment, there is activity of lupus in other organs. All too often, however, we have seen lupus nephritis as the sole organ activity. Occasionally, we have proven this by renal biopsy during pregnancy. When the urinary abnormalities occur before the third trimester, we believe this should be more strongly considered.

It can be helpful to demonstrate falling levels of C3 and/or C4, which is consistent with lupus nephritis. C3 and C4 rise during normal pregnancy and pre-eclampsia, because they are part of the acute phase reaction. Urine red blood cells or urine casts are more consistent with lupus nephritis. However, we have found biopsy-proven lupus nephritis in pregnancy with minimal findings on the urinary sediment examination.

Key Issue #8. How Should Antiphospholipid Antibodies Be Treated During SLE Pregnancy?

We believe that SLE pregnancies with antiphospholipid antibodies have worse outcomes than published clinical trials of APS pregnancies. In a first pregnancy, we usually use low dose aspirin alone. If there has been a poor past obstetric history, either pregnancy loss, pre-eclampsia, or evidence of placental insufficiency, we use LMW heparin 20 to 30 units twice daily and low dose aspirin. Because of its pharmacokinetics in pregnancy, LMW heparin should be dosed twice daily in pregnancy. Before delivery we switch to unfractionated heparin. The use of heparin now has a grounding in basic science: in a murine model, the benefit of heparin is an anti-inflammatory one, in that it blocks complement activation [25].

Unfortunately, we still encounter many pregnancy losses in spite of heparin and aspirin therapy. There is no evidence-based approach to what to do next. Two clinical trials have failed to show any added benefit of intravenous immunoglobulin [26]. If the patient does not already require prednisone for SLE activity, we often add low dose prednisone 15 mg daily during the next pregnancy.

The post-partum period is actually the greatest risk period for the mother in terms of thrombosis. We always continue prophylactic heparin for 6 weeks post-partum.

Key Issue #9. Is Death a Risk of SLE Pregnancy?

Unfortunately, the answer is “yes”. Two of my last 300 patients died post-partum: a patient with mild thrombocytopenia and no evidence of antiphospholipid antibodies had a post-partum pulmonary embolus; and a patient with lupus myocarditis died post-partum, suddenly at home.

Several other patients have had progression of renal organ damage during pregnancy, needing either dialysis during pregnancy, or dialysis post-partum.

I have also seen life-threatening complications of antiphospholipid antibodies with non-fatal but disabling strokes in spite of therapeutic anticoagulations, severe transverse myelitis, and HELLP (hemolysis, elevated liver function tests, and low platelets) syndrome.

Key Issue #10. How Often Should the Rheumatologist See the SLE Patient?

In a stable, non-pregnant patient I recommend quarterly followup. In pregnancy, however, I recommend every 4 to 6 weeks. These visits should include the interval history, the pertinent physical examination, and laboratory monitoring. The laboratory monitoring should include the complete blood count, platelet count, comprehensive metabolic panel, urinalysis with microscopic examination, C3, C4, CH50, anti-dsDNA, anticardiolipin, and uric acid. The goal is to keep the lupus quiet with acceptable medication.

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