Many Factors Influence Lupus Pregnancy Outcome

BY DIANA MAHONEY
New England Bureau

BOSTON — Successful pregnancies in women with systemic lupus erythematosus depend on a combination of factors, including disease activity at the time of conception, maternal renal function, the presence of lupus-related autoantibodies, and medication use, according to Dr. Lisa Sammaritano of Cornell University, New York.

In terms of disease activity, "it has been shown time and again that patients with inactive disease for 6 or more months prior to conception have a substantially reduced risk of experiencing a disease flare during pregnancy than women with active disease," Dr. Sammaritano said at a meeting on rheumatology sponsored by Harvard Medical School. Physicians "should have this in mind during prepregnancy consultations and advise patients to wait for periods of stable disease before trying to conceive."

Physicians should 'advise patients to wait for periods of stable disease before trying to conceive' and should assess renal function before conception.

Maternal renal function also should be evaluated prior to conception, Dr. Sammaritano said. In women with renal insufficiency, pregnancy can accelerate a decline in renal function and worsen hypertension and proteinuria, thus increasing the risk of maternal and fetal complications, such as preeclampsia, intrauterine growth restriction, and intrauterine death.

Additionally, "it's essential to assess renal function before pregnancy in women with renal insufficiency in order to better differentiate worsening lupus-related renal disease from superimposed preeclampsia during pregnancy," she said.

Kidney problems during pregnancy are more likely to be related to systemic lupus erythematosus (SLE) renal disease than to preeclampsia if the patient exhibits clinical symptoms of active SLE, has an elevated anti–double stranded DNA antibody, or has detectable red blood cell casts in the urine, she said.

The presence and levels of certain lupus-related autoantibodies can also affect pregnancy outcome, Dr. Sammaritano noted. The antiphospholipid antibodies as well as lupus anticoagulant and medium to high anticardiolipin antibodies have been associated with recurrent pregnancy losses, poor fetal growth, preeclampsia, and stillbirths in women with lupus.

Although it is unclear exactly how these antibodies affect pregnancy, "it is presumed that they can predispose the patient to blood clot formation in the placenta and impair nourishment," she said. Identifying the antibodies ahead of time "is critical, because studies have shown that treatment with medication, such as aspirin or heparin, during pregnancy can improve the viability of the fetus."

Two other lupus-related autoantibodies—anti-SS-A and anti-SS-B—can have an effect on the babies born to mothers with lupus. The presence of one or both of these IgG autoantibodies in the mother increases the risk of neonatal lupus erythematosus (NLE), which can cause rash or changes in blood counts or liver function and, in severe cases, can affect the conduction system of the heart, Dr. Sammaritano said.

"The risk of NLE is related to the presence of these antibodies specifically, not to the underlying diagnosis of SLE in the mother," she said. "Babies born to mothers who test positive for these antibodies have a 25%-30% chance of developing any manifestation of NLE."

In terms of medication during pregnancy for women with lupus, corticosteroids should be used for active disease only. "If a patient is on a dose of steroid, in general we will continue at a low dose during the course of the pregnancy. However, we do not recommend prophylactic steroids in patients without active disease in an effort to prevent a flare," she said.

For patients on immunosuppressive therapy, methotrexate and cyclophosphamide are contraindicated in pregnancy, "but azathioprine (Imuran) is an option," Dr. Sammaritano said. "Even though [azathioprine] is classified as a risk category D drug, there are no reports of fetal anomalies, and it is widely used in pregnancy."

Less is known about the safety in pregnancy of the disease-modifying antirheumatic drugs, according to Dr. Sammaritano. "Sulfasalazine is thought to be generally safe, and the minimal data that exists on the TNF inhibitors is reassuring," she said. In contrast, leflunomide is contraindicated and requires a washout period before pregnancy should be considered.

Because there is no one-size-fits-all formula for managing lupus pregnancies, one of the most important considerations is having in place a multidisciplinary management team, including a rheumatologist, a high-risk obstetrician, and a nephrologist for patients with underlying renal disease, Dr. Sammaritano said. "Communication and close monitoring can have a big impact on fetal and maternal outcome." ■

VERBATIM

Inventing 'is best done with a full stomach, which means you should not give up your medical practice.'

Dr. Robert A. Levine on how to develop an idea for a medical invention, p. 45

DRUGS, PREGNANCY, AND LACTATION

Prenatal Vitamins and Pediatric Ca Risk

There is some evidence that the use of vitamins in general and folic acid in particular may inhibit the development of some types of cancer in adults, although the data are not from randomized trials and are debated.

There are also several studies suggesting folic acid may protect against certain pediatric cancers, and a recently reported metaanalysis conducted by Motherisk found that prenatal vitamin use during pregnancy was associated with a reduced risk of some pediatric cancers.


BY GIDEON KOREN, M.D.

Several years ago, we reported the results of a study in Ontario that found an association between folic acid fortification of flour and a 50% decrease in the prevalence of pediatric neuroblastoma, an apparent protective effect.

We conducted this study after the Pediatric Oncology Group in Ontario asked us if we could identify an environmental explanation for the fewer cases of neuroblastoma in children in Ontario, a trend they first noticed in the late 1990s. This group keeps records of all the pediatric cancers in the province.

The only factor we could identify was that in 1997 and 1998, folic acid fortification of flour became compulsory in Canada, as in the United States, so virtually every citizen, unless they did not eat flour-based products, was exposed to greater levels of folic acid.

We were able to show that indeed, year by year, with the introduction of folic acid fortification of flour, there was a parallel decrease in the number of neuroblastomas diagnosed in young children in Ontario (Clin. Pharmacol. Ther. 2003;74:288-94).

Intrigued by these results, we looked into whether other investigators had arrived at similar observations about multivitamin supplementation and pediatric cancers.

We conducted a metaanalysis of all eight case-control studies published between 1994 and 2005 of prenatal multivitamin supplementation and pediatric cancer rates, comparing the rates of cancer in their children with matched controls whose mothers did not use supplements.

The studies were conducted between 1976 and 2002; all were either conducted in the United States, or included U.S. sites.

These results were presented by Ingrid Goh, a graduate student in Motherisk, at the American Society of Clinical Pharmacology and Therapeutics meeting in March 2006.

We found that for several prominent pediatric cancers—brain tumors, early-age leukemias (in the first year of life), and neuroblastomas, tumors that are believed to start in utero—the rates were substantially lower among the children of women who took prenatal vitamins containing folic acid during pregnancy.

The risk of leukemia was reduced by 36%, the risk of pediatric brain tumors reduced by 35%, and the risk of neuroblastoma by 57%—all statistically significant reductions.

The metaanalysis has limitations, including the retrospective design of the studies, and likely variations in the composition of multivitamins; it is possible that another characteristic of women who are motivated enough to take multivitamins could contribute to the lower cancer rates.

Therefore, at present, these studies show a trend and an association, but are not necessarily proof of causation.

Still, as far as we know, this is the first systematic review that has investigated such a protective effect for the use of multivitamins by pregnant women, and provides the first evidence suggesting that prenatal vitamins may have a protective effect in reducing the risk of pediatric cancer and that it may be possible to reduce the risk of certain childhood cancers in utero.

This finding is important because for the most part, not much is known about how to prevent pediatric cancers. These findings may also contribute to the understanding of the etiology of cancer.

Folic acid, for example, is involved in many intracellular processes, and it has been hypothesized that folate deficiencies and cancers in children may be related to partially altered DNA methylation and impaired DNA synthesis and repair.

Currently, we can not separate what constituents in the multivitamin are responsible for the protective effect; this will be much more difficult to sort out.

Despite the limitations of the studies in the metaanalysis, they represent another level of evidence for physicians and women that highlight the importance of prenatal supplementation with a multivitamin containing folic acid.

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