Managing Pregnancy in Rheumatic Disease Patients

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CHICAGO — The only "sure thing" about the medical management of pregnant women who have a rheumatic disease is that there are no sure things, advises a rheumatologist with particular expertise in lupus.

"In an ideal world, pregnancy in these women would always be planned; the rheumatic disease would have been in remission for at least 6 months at the time of conception, and there would be a plan for treatment if the disease flares. Unfortunately, clinical medicine isn't an ideal world," said Dr. Bonnie L. Bermas, director of the Center for Lupus and Antiphospholipid Antibody at Brigham and Women's Hospital, Boston.

Exacerbating the challenge is the absence of any one-size-fits-all management formula, Dr. Bermas said, noting that the interplay among the individual patient, disease, and treatment variables—all of which are unpredictable—drives therapeutic decisions.

With rheumatoid arthritis (RA), for example, "the literature supports that about 70%-80% of patients will go into remission during pregnancy, though most will flare post partum," said Dr. Bermas at a symposium sponsored by the American College of Rheumatology (ACR). Even though this knowledge provides clinicians with some flexibility with respect to medication during pregnancy, "we really can't predict who's going to go into remission, so we can't say up front, 'I guarantee you'll be able to go off treatment once you become pregnant,' " she said.

Systemic lupus erythematosus (SLE), on the other hand, is thought to be associated with a slightly increased risk of flare during pregnancy, said Dr. Bermas. "This means that we will approach a lupus patient differently than a rheumatoid arthritis patient in terms of our management plan, and the answers to the critical questions—'Will the disease flare? Will the baby be affected by the disease? What medications are safe to take during pregnancy?'—will be different."

Although the Food and Drug Administration's use-in-pregnancy ratings for the mainstays of rheumatic disease therapies provide a management framework, there is often a discrepancy between what the FDA says is allowable during pregnancy and what clinicians feel comfortable prescribing, Dr. Bermas said.

NSAIDs, Cyclooxygenase-2 Inhibitors

Although animal studies have shown an increased risk of congenital anomalies with these agents, "when you get to the human studies, there really is no increased risk of congenital anomalies," said Dr. Bermas. "There is an increased risk of premature closure of the ductus arteriosus in pa-

Drug Treatment Considerations

The treatment of rheumatic diseases in pregnant women should be based on disease severity and drug safety, according to Dr. Bermas, who suggested the following general guide to treatment options:

Mild Disease

► For inflammatory arthritis, Dr. Bermas recommends stopping drug therapy before pregnancy or when pregnancy is discovered.
► For SLE, maintain these patients on hydroxychloroquine.
► NSAIDS are acceptable up to week 24.

Moderate Disease

► Steroids should be used at the lowest possible dose.
► Azathioprine should be used with caution.
► Cyclosporin A should be used with caution.
► Sulfasalazine should be used with caution.

Severe Disease

► High-dose steroids should be used with caution.
► Azathioprine should be used with caution.
► Cyclosporin A should be used with caution.
► Cyclophosphamide should be used only in life-or-death situations.

tients exposed to nonsteroidals late in pregnancy, so we counsel patients that they can use nonsteroidals up to 24 weeks' gestation. We could probably protract this out to 30 weeks, but it's easier to say, 'stop the NSAIDS in the third trimester.' "

For patients trying to conceive, "we advise that they avoid using COX-2s and NSAIDs during the conception cycle because both can have an impact on implantation," Dr. Bermas noted.

Antimalarials

A single case report of congenital defects in three of four babies born to one mother who took 250 mg of chloroquine two times a day during each of her four pregnancies earned antimalarials an FDA category C rating, "which is sort of representative of how the literature about medication in pregnancy has been interpreted over the years," said Dr. Bermas. In the meantime, she said, there have been several case series in which no increased risk of congenital anomalies has been seen, and the literature on the use of these drugs as malarial prophylaxis (at higher doses than are used to treat rheumatic disease) has identified no untoward effects in pregnant women.

"For many years, we didn't use any of these drugs during pregnancy, but a recent ACR survey showed that most rheumatologists today are comfortable leaving patients on antimalarials during pregnancy," said Dr. Berman. "Having said that, if I have an RA patient whose main medication is hydroxychloroquine, that patient probably has fairly mild disease. Considering that most RA patients go into remission during pregnancy, I usually recommend stopping the drug during gestation."

But for a patient with SLE who is well maintained on hydroxychloroquine, "I'd probably keep the medication on board," because additional data show that patients with lupus who remain on therapy have better outcomes.

Steroids

For flares of most rheumatic diseases, steroids are considered "the ace in the hole," said Dr. Bermas.

"During pregnancy, if rheumatoid arthritis, for example, becomes active, most clinicians recommend starting treatment with the lowest dose possible of a glucocorticoid medication, most commonly prednisone." Both prednisone and methylprednisolone cross the placenta, but only at low levels, she said.

The data on steroid safety during pregnancy are mixed. "Originally, there were some case reports of cleft palate formation

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in offspring, although no increased risk of fetal anomalies was found in a large series of asthma patients treated with steroids throughout pregnancy," said Dr. Bermas. "In a meta-analysis of epidemiological studies, however, there was a 3.4-fold increase in the incidence of cleft palate formation associated with maternal exposure to corticosteroids [Teratology, 2000;62:385-92]," she said. "The key time frame seems to be between weeks 6 and 12, when the palate is forming."

Corticosteroids during pregnancy are also associated with maternal comorbidities, including gestational diabetes, hypertension, and accelerated osteoporosis. "For this reason, the goal should always be to keep the dose as low as possible," she said.

Azathioprine and 6-Mercaptopurine

The use of azathioprine, a nonbiologic disease-modifying antirheumatic drug, is generally limited to women with severe disease who have not responded to other treatments, Dr. Bermas stated. There are "conflicting data about the safety of this drug during pregnancy. Animal data [suggest that] the drug is teratogenic, and there have been case reports of fetal malformations, but transplant series indicate that the medication doesn't increase the rate of congenital anomalies," she said. Small-for-gestational-age babies and premature rupture of membranes are associated with use of the drug during pregnancy.

As with azathioprine, the nucleoside analog 6-mercaptopurine is teratogenic in animals, and it is plagued by conflicting human data. Some of the human studies suggest that "there is an increased risk of congenital anomalies, but the gastrointestinal literature doesn't support this," Dr. Bermas noted. "From a rheumatology perspective, this medication is rarely used, so I would suggest discontinuing it during pregnancy."

Sulfasalazine

"Case reports of fetal malformations linked to sulfasalazine from the inflammatory bowel disease literature didn't pan out in larger studies," said Dr. Bermas. "This drug can be used in pregnancy. It does cause azoospermia in men, however, so if you have a male patient who is interested in trying to get his partner pregnant, advise him to stop taking sulfasalazine for 3 months before conception for spermatogenesis."

Penicillamine

Occasionally used in the treatment of progressive systemic sclerosis, penicillamine

has been shown to interfere with collagen biosynthesis and to cause malformations in animal studies, according to Dr. Bermas. "In humans, cases of cutis laxa and connective tissue disorders have been reported with exposure to this medication," she said. As such, "this medication should not be used during pregnancy."

Mycophenolate Mofetil

"We had such high hopes for mycophenolate mofetil. We thought this would be one of those medications that could be safely used during pregnancy," said Dr. Bermas. "Unfortunately, there are increased case reports of congenital anomalies, including one report of the drug being used during pregnancy in a renal transplant patient. The baby was born prematurely and was noted to have hypoplastic nails and short fifth fingers." Although there is not a rich body of literature yet, "this medication should be avoided during pregnancy," she said.

IVIG

Intravenous immunoglobulin is not a common drug for rheumatologic disorders, and the literature on its use in pregnancy is limited. "In one case report of an individual with steroid-resistant idiopathic thrombocytopenic purpura, IVIG was used with no adverse effects on the offspring," said Dr. Bermas. "The medication has also been used to manage the obstetrical complications of the antiphospholipid antibody syndrome without inducing congenital malformations." Based on the available data, IVIG, when warranted, is acceptable for use in pregnancy, she said.

Cyclosporin A

The large body of data regarding the use of cyclosporin A during pregnancy comes from the transplant literature. "These medications are not teratogenic, although they are associated with small-for-gestational-age infants and hypertension of pregnancy," said Dr. Bermas. The drug is not widely used, but in individual cases, if the potential benefit outweighs the possible risk, clinicians may choose to continue treatment with it, she noted.

Chlorambucil and Cyclophosphamide

Both of these cytotoxic agents are teratogenic and should be avoided during pregnancy, Dr. Bermas stressed. "In life-or-death situations, cyclophosphosamide has been used in the third trimester," she said.

Methotrexate

Because of the high risk of congenital anomalies, methotrexate is an FDA category X drug for use in pregnancy. In addition to being teratogenic, it is also abortifacient, said Dr. Bermas, noting that, in terms of gestation, the use of methotrexate during weeks 6-8 at dosages greater than 10 mg/day substantially increases the risk of fetal harm. "I recommend that patients, both men and women, discontinue methotrexate for at least 3 months prior to conception," she said.

Leflunomide

Another FDA category X drug for use in pregnancy because of its high teratogenicity, leflunomide "has an extremely long half-life, so either you need to wash out with cholestyramine or discontinue for 2 years before conception," said Dr. Bermas. "As a general rule, I avoid using this in women of childbearing potential."

Anti-TNF-α Agents

Limited data exist regarding the safety of the tumor necrosis factor–α inhibitors during pregnancy, "although case reports of two infants exposed to these drugs in utero being born with anomalies potentially consistent with VACTERL [vertebral, anal, cardiac, tracheal, esophageal, renal, and limb] syndrome give clinicians pause," said Dr. Bermas. On the other hand, animal studies reported no teratogenic or fetotoxic effects, and some reports on human pregnancy in patients taking these drugs did not show an increase in birth defects or adverse pregnancy outcomes, she said. In one large study comprising 131 patients with inflammatory chronic diseases—including 8 patients with RA—who were directly exposed to infliximab, drug exposure during pregnancy resulted in outcomes similar to those seen in the general population of pregnant women (Am. J. Gastroenterol, 2004;99:2385-92).

Rituximab

More commonly used for the treatment of non-Hodgkin's lymphoma, rituximab is also used for patients with refractory RA. Although as of yet there are no reports of congenital anomalies associated with this anti-CD20 monoclonal antibody, "there are insufficient data regarding the safety of the drug in animal or human pregnancy," said Dr. Bermas. Two case reports of successful outcomes in women treated with rituximab for non-Hodgkin's lymphoma during pregnancy are promising, but not yet representative, she said. In fact, given the availability of safer alternative medications for pregnant RA patients, along with the possibility of remission during pregnancy, rituximab should probably be avoided unless there's a compelling reason to use it, she said. ■