Maintain Hydroxychloroquine in APS in Pregnancy

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DESTIN, FLA. — Pregnant women with antiphospholipid syndrome need anticoagulation throughout pregnancy and for at least 6 weeks post partum, Dr. Ann Parke said at the annual Rheumatology on the Beach.

Low-dose aspirin can also be added to anticoagulant therapy. The antimalarial drug hydroxychloroquine should be continued in those with systemic lupus erythematosus (SLE), said Dr. Parke, professor of medicine at the University of Connecticut, Farmington.

Discontinuing hydroxychloroquine will put the patient at risk of an SLE flare, putting the pregnancy and patient in jeopardy. SLE flares, as well as pregnancy, are among the known "second hit" phenomena that can trigger thrombosis in patients with antiphospholipid antibodies, Dr. Parke said. (See related story.)

Furthermore, data suggest that this drug—which reverses platelet activation induced by human IgG anticardiolipin, and which has been shown to reduce thrombosis size in antiphospholipid animal models—is safe in pregnancy, she added.

Other treatments used in pregnant patients with antiphospholipid syndrome (APS) include corticosteroids and intravenous immunoglobulin. IVIG is expensive, and there is no clear evidence of benefit, said Dr. Parke. Corticosteroids, which lost favor because of associated increases in maternal morbidity and risk of preterm birth, may regain ground in light of new evidence that complement activation plays a role in antiphospholipid antibody–associated placental injury. (See box.)

Pregnant patients with APS should be monitored closely for signs of placental insufficiency, HELLP (hemolytic anemia, elevated liver enzymes, low platelet count) syndrome, and toxemia, she said, noting more than 80% of women with APS experience at least one fetal death; in fact, the specificity of fetal death for the presence of antiphospholipid antibodies is 76%.

As for the treatment of pregnant patients with antiphospholipid antibodies who don't meet the criteria for antiphospholipid syndrome, a literature review published last year (JAMA 2006;295:1050-7) suggested asymptomatic patients and those who have experienced a single fetal loss before 10 weeks' gestation should receive no treatment, and that those with recurrent losses but no clinical thrombotic event should receive low-dose aspirin and prophylactic heparin throughout pregnancy and for a minimum of 6 weeks post partum. (Dr. Parke said she suspects this will be increased to 4 months because recent evidence suggests the risk of thrombosis is high throughout the first postpartum year.)

Like her recommendations for those with APS, the findings from the literature review supported the use of low-dose aspirin and therapeutic heparin throughout pregnancy, plus long-term warfarin post partum in those with recurrent losses and a clinical thrombotic event (who thus meet current Sapporo Criteria for APS).

Warfarin use, however, depends on the nature of the antibodies present. Lupus anticoagulant is more likely to be associated with clinical events than is anticardiolipin, for example. Titer, persistence, and isotype of the antibodies; the number of positive antibodies; and the presence of additional risk factors, such as SLE, also play into the decision to prescribe warfarin. A number of studies have shown moderate warfarin doses are as effective as and safer than high doses in such patients. It remains unclear whether it is necessary to use warfarin in patients with antibodies who have a clinical thrombotic event triggered by second hit phenomenon, she said.

Other issues not adequately addressed include therapy for patients with antibodies but no clinical event, optimal therapy for noncerebral artery thrombosis, managing patients who have recurrence despite adequate international normalized ratios, and therapy in women with antibodies and recurrent fetal losses. ■

Studies Probe APLA, Complement Links

Animal studies show preventing complement activation is essential in pregnancy, and deficiencies of certain complement components in the presence of antiphospholipid antibodies (APLA) prevent fetal death. Inhibitors of these components are protective in antibody-exposed mice. A study of human placentas suggests complement activation plays a role in APLA-associated placental injury, Dr. Parke said.

Using immunohistochemical methods to identify deposition of complement activation products in the placentas of 47 full-term viable pregnancies in women with APLA and 23 control placentas, investigators showed those with antibodies had more deposition of complement components C4d, C3b, and C5b-9 in the villous trophoblast cytoplasm and the extravillous trophoblast of the basal plate, and deposition of C4d in the trophoblastic cell and basement membrane (Am. J. Obstet. Gynecol. 2007;196:167).

Immunoreactivity was stronger for the C4d protein in all three areas in the APLA placentas and for the C3b protein in the villous trophoblast cytoplasm in the APLA placentas, versus controls. A link was seen between pathologic lesions and the deposition of C4d in the trophoblast cytoplasm and cellular and basement membranes.

In light of prior data showing trophoblastic cell membranes are targets for APLA, and the finding that placental lesions in women with these antibodies are tied to malperfusion, it seems "proinflammatory factors that stimulate complement activation may precede the changes that ultimately lead to ischemia, tissue injury, and fetal loss," they wrote.

The deposition of complement activation products in patients with antibodies occurs because the protection provided by complement regulatory proteins is overwhelmed by antibodies. This deposition is likely due to increased activation of the complement system, rather than a depletion or inactivation of the complement regulatory proteins.

'Second Hits' Trigger Problems In Antiphospholipid Syndrome

DESTIN, FLA. — The fact that some patients have antiphospholipid antibodies for years and only develop clinical problems under certain conditions has given rise to the theory that a "second hit" is sometimes required to trigger antiphospholipid syndrome, Dr. Ann Parke said at the annual Rheumatology on the Beach.

Second hit phenomena include pregnancy, exogenous estrogens, flares of systemic lupus erythematosus (SLE), infection and inflammation, surgery, and vascular procedures or trauma. All may promote thrombosis in these patients, said Dr. Park, professor of medicine at the University of Connecticut, Farmington. These conditions and circumstances interfere with normal anticoagulant pathways, in particular the protein C and S pathways known to be associated with antiphospholipid syndrome (APS). Patients with antiphospholipid antibodies should notify physicians if they become pregnant or if they are to undergo surgery or vascular procedures.

Those undergoing surgery must be adequately anticoagulated perioperatively and maintained on low-molecular-weight heparin as necessary. In those with SLE, flares should be controlled and monitored.

It is also important that patients with antiphospholipid antibodies be warned of risks associated with use of exogenous estrogens, Dr. Park said.

Infection is the most worrisome of the second hit factors, because it is the least controllable. Patient education about preventing infection is critical, she said.

—Sharon Worcester