

Watch Fetus In Presence of Anti-Ro/La Antibodies

BY NANCY WALSH
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NEW YORK — Any pregnant woman who has anti-Ro/La antibodies should have weekly fetal echocardiograms beginning at 16 weeks' gestation to look for possible signs of congenital heart block, Dr. Jill P. Buyon said at a rheumatology meeting sponsored by New York University.

During pregnancy these autoantibodies, which are typically found in high titers in patients with systemic lupus erythematosus (SLE) and Sjögren's syndrome, but also in some asymptomatic individuals, begin to cross the placenta as early as 11 weeks.

The autoantibodies accumulate in the fetal circulation and are associated with the development of various manifestations of neonatal lupus, particularly prolongation of the mechanical PR interval and congenital atrioventricular block.

The importance of early detection of these autoantibodies in the fetus is underscored by the fact that once third-degree, or complete, heart block has developed, it is irreversible with current therapies, according to Dr. Buyon, professor of medicine, department of rheumatology, New York University, New York City.

Moreover, anti-Ro/La congenital heart block carries a 20% mortality, and at present the majority of children who survive need a pacemaker.

Intense research interest therefore is focused on identifying markers of early cardiac injury, at a point before fibrosis and scarring are permanent, and on the potential for therapeutic interventions to reverse early changes.

The use of cardiac monitoring to detect prolongations of the PR interval greater than 150 milliseconds was recently evaluated in the observational PR Interval and Dexamethasone Evaluation (PRIDE) study of pregnant women who were positive for anti-Ro and/or anti-La antibodies. The study also attempted to

provide some data on outcomes following the administration of steroids.

Fetal echocardiography was performed weekly between weeks 16 and 26, and then biweekly between weeks 26 and 34, according to Dr. Buyon, one of the study investigators.

She and her colleagues were looking for prolongation of the PR interval, evidence of tricuspid regurgitation, and unexplained atrial echodensities.

Among the 88 patients who completed an evaluable course, there were three cases of third-degree heart block.

One of these patients had a normal PR interval, but some tricuspid regurgitation was noted at 17 weeks and atrial echodensity, at 22 weeks.

A week later the fetus was in third-degree heart block and, despite treatment with maternal dexamethasone, 4 mg/day, severe hydrops developed and the pregnancy was terminated.

The second fetus had a normal PR interval between weeks 16 and 18 along with mild tricuspid regurgitation at week 17. The mother missed an appointment and, by the next time she was seen, third-degree block had developed in the fetus. This persisted despite administration of dexamethasone, and the child continued to be followed after birth (*Arthritis Rheum.* 2006;54:S689).

The third fetus also had a normal PR interval at 18 weeks, but 10 days later the fetus was in third-degree block and hydropic. Treatment with dexamethasone was unsuccessful, and the pregnancy was terminated at 20.5 weeks.

First-degree block was detected in an additional three fetuses. In one, the PR was normal at weeks 16-18, was prolonged at week 19, and normalized within 7 days of dexamethasone treatment.

The second had a prolonged PR interval at week 22 that resolved within 3 days of dexamethasone treatment. These two patients both had normal electrocardiograms at birth.

a genetically susceptible patient, probably in response to minor trauma, Dr. Levine said.

A proliferative fibrotic reaction results in an inelastic scar. Disturbances of collagen and elastin are seen, along with overexpression of cytokines such as transforming growth factor- β and imbalances of nitric oxide and nitric oxide synthase.

The standard treatment is surgery, but that must wait until the disease stabilizes and pain ceases. In the interim, and for patients unwilling to undergo surgery, therapies based on current thinking about pathogenesis can help.

"In a survey we did in Chicago, the most commonly used remedies were vitamin E and Potaba," said Dr. Levine, of the

department of urology at Rush Presbyterian-St. Luke's Medical Center, Chicago. Yet studies have found no benefit for vitamin E and only reduction in plaque size for the antifibrotic Potaba (aminobenzoate potassium). Colchicine, tamoxifen, and carnitine also have been found ineffective.

"The two oral agents I use are pentoxifylline and L-arginine," he said. Pentoxifylline, given in a dose of 400 mg three times a day, is inexpensive, has low toxicity, and appears to have antifibrotic activity. L-arginine is an over-the-counter amino acid that is a precursor to nitric oxide and has been shown in vitro to have antifibrotic activity. The dosage is 500 mg twice a day.

Another approach is injection

therapy. Steroids and superoxide dismutase have been tried and found to be ineffective or toxic. Studies have shown verapamil can reduce fibroblast proliferation, resulting in reduced production of collagen and other extracellular matrix macromolecules, he said at the meeting, which was cosponsored by the International Society for the Study of the Aging Male.

Uncontrolled studies have suggested up to 60% of patients can be helped with verapamil injections. "I use a multiple puncture technique with a short, five-eighths inch, 25-gauge needle.

"You don't want to use a smaller needle for fear of snapping it off in the scar," he said. Verapamil 10 mg is mixed with 6 cc of saline to give a total volume of 10

are at much higher risk of having another child with congenital heart block than are mothers positive for anti-Ro/La who have not already had an affected child.

Participants will be given 400 mg/kg of IVIG every 3 weeks for a total of five treatments between weeks 12 and 24 of pregnancy. If fewer than three fetuses develop second- or third-degree heart block, another 35 women will be enrolled.

"Then, if there are fewer than six cases of heart block out of 54, we will be on the way to having a prophylactic therapy," said Dr. Buyon, who is principal investigator for the trial.

Additional information about the PITCH trial is available online at <http://clinicaltrials.gov/show/NCT00460928>.

Next: IVIG for Heart Block Prevention?

Intravenous immune globulin (IVIG) has a history of safely being used in pregnancy, primarily for autoimmune thrombocytopenia and immune deficiency syndromes. A few cases of successful use in congenital heart block have also been reported.

To determine if this prophylactic approach could reliably decrease the placental transport of anti-Ro/SSA and anti-La/SSB antibodies, the Preventive IVIG Therapy for Congenital Heart Block (PITCH) trial is now enrolling patients. Sponsored by New York University School of Medicine and the Alliance for Lupus Research, the trial aims to enroll 19 women who are antibody positive and have already had a child with congenital heart block or a rash that might have been neonatal lupus. Such mothers

The third fetus had normal PR intervals throughout gestation but an electrocardiogram at birth showed first-degree block that has persisted to age 3 years.

Dexamethasone was also used in nine cases of second-degree block. Of these, four fetuses progressed to third-degree block, four remained in second, and one was born in normal sinus rhythm. "This was a little disappointing," Dr. Buyon said.

Of the 79 neonates for whom birth electrocardiograms were available, 78 were normal, and all 46 for whom 1-year follow-up electrocardiograms were available were normal, she said.

In conclusion, the study suggests the following, according to Dr. Buyon:

- ▶ First-degree block in utero is reversible with dexamethasone, but if present at birth, close observation by a cardiologist is needed because of the possibility of later progression.
- ▶ There has not been evidence of con-

duction abnormalities developing later in neonates whose electrocardiogram was normal at birth.

- ▶ Advanced cardiomyopathy can occur within 7 days of a normal PR interval, so even a weekly evaluation may not always be sufficient.
- ▶ Tricuspid regurgitation may be an important early marker of injury.

Dexamethasone treatment poses significant hazards to both mother and fetus, with maternal risks including diabetes and hypertension, and fetal risks including intrauterine growth retardation, adrenal suppression, and decreased brain growth. Moreover, as was seen in PRIDE, efficacy is hardly guaranteed.

Accordingly, other therapeutic approaches are currently being investigated, including inhibition of transforming growth factor- β to limit fibrosis and prophylaxis with intravenous immune globulin (see box). ■

Medical Therapies Stabilize, but Not Cure, Peyronie's Disease

BY NANCY WALSH
New York Bureau

MONTREAL — There is no cure for Peyronie's disease, but management can offer patients stabilization in its early phase, Dr. Laurence A. Levine said at a congress sponsored by the Canadian Society for the Study of the Aging Male.

The condition, first reported by Francois de la Peyronie in 1743, is characterized by the development of a penile plaque in the tunica albuginea of the corpora cavernosa. Deviation, shortening, and an hourglass-like shape can result. During the early inflammatory phase of the disease, patients can experience pain with erection.

Peyronie's disease is a disorder of wound healing that occurs in

cc, and the usual course of treatment is 12 injections at 2-week intervals.

Intralesional interferon has been used with some benefit, but "it does not appear to be as robust as what we see with verapamil," he said.

Topical verapamil is popular. Manufacturers are making substantial claims about its efficacy, but there is no published evidence of benefit, according to Dr. Levine.

It does not penetrate into the tunica albuginea, he said.

Medical therapies also can be used in conjunction with mechanical stretching. Since studies have shown 50% of patients worsen with no treatment, it's important to treat early, Dr. Levine added. ■

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