First-Trimester Screening Works Well in Clinics

BY ROBERT FINN
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RENO, NEV. — First-trimester aneuploidy screening is practical not just in the context of clinical trials but also in the everyday world of the clinic, according to a poster presented by Sriram C. Perni, M.D., and colleagues at the annual meeting of the Society for Maternal-Fetal Medicine.

Among 2,515 women evaluated at a single institution, trisomy 21 was detected in 91% of 22 pregnancies when the false-positive rate was set to 5% and in 77% of 22 pregnancies when the false-positive rate was set to 1%.

In that same group, trisomy 18 was detected in all eight affected pregnancies, whether the false-positive rate was set to 5% or 1%.

Aneuploidy screening in the first trimester relies on an algorithm incorporating four pieces of data: maternal age, blood levels of pregnancy-associated plasma protein A (PAPP-A), blood levels of free -human chorionic gonadotrophin (free –hCG), and ultrasound measurements of fetal nuchal translucency, Dr. Perni said.

A large, multicenter, clinical trial involving 8,514 patients found this algorithm to have a good sensitivity and an acceptable false-positive rate (N. Engl. J. Med. 2003;349:1405-13).

But it remained unclear whether the algorithm would perform as well in the real-world setting of a single institution, reported Dr. Perni and his colleagues at Weill Medical College of Cornell University, New York.

At their clinic, 4,883 pregnant women, who together had 5,167 fetuses, were offered first-trimester aneuploidy screening, and 2,515 women agreed.

Of those pregnancies, there were a total of 37 aneuploid fetuses—1 with trisomy 13, 8 with trisomy 18, 22 with trisomy 21, 4 with 45X, 1 with 47XXY, and 1 with triploidy.

Of the 22 cases of trisomy 21, 3 resulted in a live birth, and 19 were electively terminated. All eight fetuses with trisomy 18 were electively terminated.

Asked in an interview whether first-trimester aneuploidy screening remained controversial, Dr. Perni replied, "I don't think it's controversial, but right now it's not the standard of care. There needs to be more evidence that it's reproducible at a single institution like this.

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"This is a very, very good test," continued Dr. Perni, who disclaimed any financial interest in the test.

"It can be done very early and has a very good detection rate for fixed false-positive rates," he said.

He said that many insurance carriers in New York City do cover the screening test. And while the test has become "almost the standard of care" in certain parts of the United States, "it just hasn't become vogue over the whole country."

He added, "I think the most exciting thing about this is that we can get information for couples and women specifically very early on to help them determine what they want to do." ■

Large Study Confirms Benefit of Oral Tocolysis Maintenance

RENO, NEV. — While many physicians commonly use oral tocolysis maintenance after intravenous tocolysis in patients with preterm labor because they have a clinical impression of its effectiveness, solid evidence for this practice has been lacking until recently, according to Perkin Stang, M.D., of Wayne State University, Detroit, and colleagues.

Their population-based historical cohort study suggests that pregnant patients who are not maintained on oral tocolysis are more than twice as likely to deliver prematurely as are those who do receive oral maintenance, the investigators reported in a poster presentation at the annual meeting of the Society for Maternal-Fetal Medicine.

The study involved 170,258 patients from a perinatal database in the state of Schleswig-Holstein, Germany.

Of those patients, 9,542 with preterm labor who received intravenous tocolysis were included in the study. Women with premature rupture of membranes and medically indicated inductions before 37 weeks of gestation were excluded from the analysis.

Investigators compared 4,936 women who received oral maintenance tocolysis with a –sympathomimetic agent to 4,536 women who did not receive oral tocolysis. (Data were unavailable for the remaining 70 patients.)

In the oral tocolysis group, 366 patients (7%) delivered prematurely versus 1,094 patients (24%) in the control group.

After adjusting the results for possible confounding variables such as prior preterm delivery, cerclage, incompetent cervix, duration of intravenous tocolysis, and obesity, investigators calculated an odds ratio of 2.4 for preterm delivery in patients who were not maintained on oral tocolysis.

—Robert Finn

DRUGS, PREGNANCY, AND LACTATION

Rheumatoid Arthritis Drugs

The autoimmune disorder rheumatoid arthritis occurs in about 1%-2% of the population. The disease is more prevalent in women than men by about a 3:1 ratio, but in the reproductive years, the ratio may be as high as 6:1. During pregnancy, the incidence is about 1:1,000.

RA is characterized by the production of cytokines, including tumor necrosis factor– (TNF-) and interleukin-1 in the synovial cavity, and irreversible damage to soft tissues and bones. Drug therapy of RA involves the use of disease-modifying antirheumatic drugs (DMARDs) to prevent or lessen this damage. The therapy can be categorized as biologic DMARDs, synthetic DMARDs, and anti-inflammatory agents.


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Biologic DMARDs include three agents that inhibit TNF- —adalimumab (Humira), etanercept (Enbrel), and infliximab (Remicade)—and one interleukin-1 receptor antagonist, anakinra (Kineret). Although the human pregnancy data for these four drugs are very limited or completely absent, animal reproduction data suggest they pose a low risk for developmental toxicity (growth retardation, structural defects, functional/behavioral defects, or death).

The safest course is to avoid these agents during the first trimester, but with their long elimination half-lives, inadvertent exposures during organogenesis of unplanned pregnancies is likely.

The synthetic DMARDs include azathioprine (Imuran), cyclosporine (Sandimmune, Neoral), gold compounds, hydroxychloroquine (Plaquenil), leflunomide (Arava), methotrexate, penicillamine, and sulfasalazine (Azulfidine).

The immunosuppressants, azathioprine and cyclosporine, do not appear to cause congenital defects, but may be associated with growth retardation. There is limited human pregnancy experience with the gold compounds—auranofin (Ridaura), aurothioglucose (Solganal), and gold sodium thiomalate (Aurolate)—but the animal data suggest the risk for developmental toxicity is low.

Hydroxychloroquine is probably compatible in pregnancy. However, there is limited pregnancy experience with the high doses commonly used in RA. The drug has a very long elimination half-life from maternal tissues (weeks to months). Thus, stopping the drug when pregnancy is confirmed will not prevent embryo/fetal exposure.

Leflunomide, a pyrimidine synthesis inhibitor, causes dose-related teratogenicity and toxicity in animals at doses much lower than those used in humans. Human pregnancy experience is too limited to determine the risk to the embryo or fetus, and the drug is contraindicated in pregnancy. Exposure of unplanned pregnancies will probably occur because the drug and its active metabolite may take up to 2 years to reach nondetectable plasma levels.

The folic acid antagonist methotrexate is contraindicated during pregnancy. The drug is associated with spontaneous abortions and a spectrum of congenital defects collectively termed methotrexate embryopathy. The critical exposure period for structural defects is 8-10 weeks after the first day of the last menstrual period. Exposure after this period is associated with fetal toxicity and mortality. The critical dose is thought to be 10 mg or more per week.

Another folate antagonist, sulfasalazine, does not appear to cause developmental toxicity, but supplemental folic acid (1 mg/day) should be used if there is a risk of unplanned pregnancy or if pregnancy occurs. The drug has caused bloody diarrhea in a nursing infant, so breast-feeding should be undertaken cautiously. Penicillamine, a chelating agent, is linked with a risk of fetal connective tissue defects (cutis laxa) and should be avoided during pregnancy.

The anti-inflammatory agents include prednisone and the nonsteroidal anti-inflammatory drugs (NSAIDs), which include aspirin. There is considerable potential for embryo/fetal toxicity from NSAIDs: spontaneous abortions when used around the time of conception, fetal renal toxicity, and premature closure of the ductus arteriosus in the third trimester. Aspirin use near term may increase the risk of bleeding in the mother and the infant. The use of prednisone during organogenesis carries a low risk for oral clefts and prolonged use in pregnancy has been associated with growth retardation.

The biologic DMARDs, gold compounds, hydroxychloroquine, NSAIDs (except high-dose aspirin), and prednisone are likely compatible with breast-feeding. The other agents are contraindicated (methotrexate) or should be avoided due to potential toxicity.

The Organization of Teratology Information Services is conducting a study of pregnancy exposure to rheumatoid arthritis drugs. Health care professionals may call toll-free (877-311-8972) for information on enrolling patients in this study.

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