AFP Testing Deemed Expensive, Obsolete

BY DAMIAN McNAMARA
Miami Bureau

MIAMI BEACH — Maternal serum α-fetoprotein is no longer an effective or cost-effective second-trimester screen for neural tube defects in an era when women routinely undergo first-trimester Down syndrome screening and subsequent ultrasound, Dr. Todd J. Rosen said at the annual meeting of the Society for Maternal-Fetal Medicine.

Before ultrasound was commonplace—back in the 1970s and 1980s—women got an α-fetoprotein (AFP) test for spina bifida and anencephaly. "Now more and more women are screening for Down syndrome in the first trimester, and it is routine for women to do an ultrasound screen as well," said Dr. Rosen of the division of maternal-fetal medicine, Columbia University, New York.

Dr. Rosen and his associates assessed clinical and cost effectiveness of AFP testing for U.S. women who had a first-trimester Down syndrome risk assessment and second-trimester ultrasound examination. They used a decision analysis model that assumed ultrasound provides 100% detection of anencephaly and 92% detection of spina bifida (the lowest percentage reported in the literature). To put AFP testing in the most favorable light, the model assumed a 92% detection rate for spina bifida (the highest in the literature) with a 3% false-positive rate.

The model predicted an estimated 4,000 neural tube defects among the approximate 4 million births in the United States in 2003. Screening of all these women with ultrasound would detect 2,208 of the 2,400 cases of spina bifida. AFP testing would yield 120,000 positive results and detect 176 of the 192 cases of spina bifida missed by ultrasound.

"The AFP test induces anxiety—for every 10,000 women who screen positive, only 3 will have a baby with spina bifida," Dr. Rosen said. AFP screening in women who undergo first- and second-trimester ultrasound examinations has a poor predictive value and causes more pregnancy losses from amniocentesis than cases of spina bifida it detects, he added. In addition, "by continuing to do AFP, we are spending all this money," Dr. Rosen said.

For example, universal screening in the study cohort would cost $184 million. Because about 40% of women terminate a pregnancy because of spina bifida (in this model, 70 of 176 women), the cost becomes $2.6 million for each case prevented. Assuming that 50% of women with an elevated AFP result have amniocentesis and that the procedure's loss rate is one fetus per 250, 245 women would lose their pregnancies, he estimated.

"As doctors we are really caught. We want to do what is right for patients, but we have a high risk of malpractice [lawsuits]," Dr. Rosen said. "Because we are so wary of missing anything, we err on the side of overtesting and this can do more harm than good." ■

Consider Hydroxychloroquine Continuation in Lupus Pregnancy

BY TIMOTHY F. KIRN
Sacramento Bureau

SNOWMASS, COLO. — Lupus treatment should not be discontinued in anticipation of a pregnancy, Dr. W. Joseph McCune said at a symposium sponsored by the American College of Rheumatology.

Terminating drug treatment results in flares, and it is now clear that "there is really nothing worse for a lupus pregnancy than a flare, either immediately before the pregnancy or during the pregnancy," said Dr. McCune, director of rheumatology outpatient services at the University of Michigan, Ann Arbor.

The use of hydroxychloroquine during pregnancy in lupus patients is receiving increased interest from specialists, he said.

Instead of cessation of therapy, many physicians are trying to continue their patients on a corticosteroid (when necessary) and hydroxychloroquine, with informed consent and disclosure that the drug is known to cross the placenta.

Hydroxychloroquine is a drug that is not the most potent agent for resolving manifestations of lupus, but one that is very good at preventing serious disease developments and flares, Dr. McCune said.

Antimalarials have a number of potentially beneficial side effects, such as improving glucose tolerance, noted Dr. McCune, who previously reviewed and reported on evidence suggesting that antimalarials positively affect both cholesterol levels and thrombosis in lupus patients who have increased cardiovascular risk.

There have been no apparent, adverse, fetal effects, and "in general, the experience has been that there have been no difficulties using this drug," in recent reports of approximately 300 lupus patients treated with hydroxychloroquine during pregnancy, Dr. McCune said.

The reports come from various series as well as a blinded, placebo-controlled clinical trial.

In the 20-patient clinical trial, none of the 10 treated patients developed toxemia of pregnancy, while 3 of the 10 patients in the placebo group did.

Moreover, the infants of the treated mothers had a greater average delivery age and had a better average Apgar score. The hydroxychloroquine-treated mothers used less prednisone (Lupus 2001;10:401-4). ■

DRUGS, PREGNANCY, AND LACTATION

Valproic Acid

For more than 20 years, the risk of neural tube defects (NTDs) associated with first-trimester exposure to valproic acid has been well known: The estimated risk is 2%, about 10- to 20-fold higher than the baseline risk. With more widespread use of valproic acid, partly due to increasing use of the drug for psychiatric conditions, more data and larger controlled studies on its teratogenic effects have accumulated over the past 3-4 years, revealing an association with major malformations that previously had been reported anecdotally. The main anomalies that have been identified are cardiac and limb malformations.

BY GIDEON KOREN, M.D.

The results reflect what we found in a metaanalysis of data from 13 cohort studies in the medical literature. The studies in the metaanalysis, which will be published this month in a Canadian journal, compared rates of major malformations among women who reported taking valproic acid during the first trimester with rates among pregnant women who were taking other antiepileptic drugs (AEDs) and among women who were not taking any such drugs.

Nearly 1,000 pregnant women were exposed to valproic acid in the 13 studies. The risk of major malformations, including NTDs, associated with exposure to valproic acid was twofold greater than the risk with exposure to other AEDs. The risk was 4.4-fold greater than in the healthy controls, representing a highly significant increase in risk among valproic acid–exposed pregnancies.

We could not include three studies comparing the neurobehavioral risks of in-utero exposure to valproic acid and other AEDs in the metaanalysis, because of their different designs and the variety of cognitive tests used. Still, all three reported an association between valproic acid and developmental delays and cognitive deficits. The most prominent effect was on verbal IQ. More studies on the neurodevelopmental effects of in-utero exposure that control for maternal education and other confounding factors need to be conducted to further examine these associations.

On the positive side, in 3 of the 13 studies that also looked at the dose-dependent effects of valproic acid, the threshold dose needed to cause malformations was about 1,000 mg/day, which has been reported over the past few years. This is true for all malformations associated with valproic acid, including NTDs. In one study, first-trimester valproic acid plasma levels in women were higher among those who had a child with a malformation; in another, a daily dose of 1,000 mg was associated with a significantly increased risk for major malformations, especially NTDs; and in the third, mothers who had a child with spina bifida were on a mean dose of 1,640 mg/day vs. a mean of 941 mg/day among those whose children had no malformations. The same studies indicated that at a dose of less than 600 mg/day, there was no increased risk.

These relatively new findings of major malformations other than NTDs and the potentially increased risk of cognitive effects of valproic acid are important for women and physicians to consider when women are planning a pregnancy. Sometimes, women who have been on a drug for epilepsy for many years may no longer need it. If a switch to another drug is not possible, patients need to be monitored closely for malformations, as has been the practice for NTDs, although there is no way to monitor for potential cognitive effects.

Another approach for women who are dependent on valproic acid is to make every effort to keep the daily dose at 600 mg or below or, if that is not feasible, under 1,000 mg/day. Patients should be monitored with ultrasound, fetal echocardiography, and maternal and amniotic α-fetoprotein testing.

Evidence that reducing the dose can be effective in reducing malformations was provided by a report last year from the Australian pregnancy registry for women on AEDs, which found the risk of fetal malformations was 13 times higher among women taking more than 1,100 mg of valproic acid per day as monotherapy, compared with women not taking an antiepileptic drug. Although the malformation rate among those on lower doses was greater than the 2%-3% risk in the general population, the difference was not significant.

If possible, a different medication for controlling seizures should be considered. Carbamazepine (Tegretol) is considered by many neurologists and obstetricians to be the AED of choice in pregnancy, because the data to date do not reveal any risks of major malformations, except for spina bifida at about 1%, which is half the rate associated with valproic acid. There are fewer data on the reproductive risks of newer antiepileptics, such as lamotrigine and gabapentin. Of all the newer drugs, lamotrigine appears to be the most promising in terms of adverse fetal outcomes, but the number of pregnancies with data is much smaller than is available with valproic acid and carbamazepine.

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