Drugs, Pregnancy, And Lactation

Autism and Exposure to Thimerosal

The etiology of autism is not yet clear and the debate continues about whether the increase in prevalence noted in the past few decades is actual or is because of better diagnosis. However, the evidence for a genetic link is accumulating, as is evidence that mercury in vaccines is not behind the increased prevalence.

Because the disease appears in the second or third year of life, the potential association with early childhood vaccines has been the subject of many studies over the past 15-20 years. Children receive many vaccines during the first few years of their lives; until 2002, thimerosal, a preservative that contains ethylmercury, was used as a preservative in routine early childhood vaccines. To a lesser degree, prenatal exposure to Rh immune globulin—which, until 2001 in the United States, contained thimerosal—has also elicited concern. Because organic mercury is a proven developmental neurotoxin, exposure to it in utero or in early childhood has raised concerns.

BY GIDEON KOREN, M.D.

In utero exposure to mercury in environmental accidents, especially organic mercury, has been associated with brain damage and pediatric diagnoses such as cerebral palsy—but not autism. Some of the most compelling evidence indicating that vaccines containing thimerosal are not a cause of autism was provided in studies that looked at population-based databases of children in Denmark, Sweden, and California.

Although the prevalence of autism increased in all three places from 1985 through the 1990s, the average exposure to vaccines containing mercury increased only in the United States. In Sweden and Denmark, where the use of mercury-containing vaccines began to decrease in the late 1980s and was eliminated by the early 1990s, there was still an increase in the diagnosis of autism.

An important study published last month provides compelling evidence that prenatal exposure to thimerosal in Rh immune globulin is not a likely cause of the increase in autism, either. These results should help allay lingering concerns about exposure to ethylmercury via thimerosal in vaccines and Rh immune globulin.

The new study analyzed records of families that have children with an autism spectrum disorder (ASD), who had been seen at the Thompson Center for Autism and Neurodevelopmental Disorders at the University of Missouri–Columbia, between 2004 and 2006. Of 214 mothers with 230 children diagnosed with ASD between 1995 and 2005, 33 (15.4%) were Rh negative, which was similar to the rates among mothers in control groups. Of these 33 women, 29 (88%) had received Rh immune globulin that contained thimerosal while pregnant.

Based on comparisons with families of children with Down syndrome and other de novo chromosome disorders who came to the university for care, and two other populations—patients blood typed at the hospital in 2005 and 2006, and a population who had donated blood during 2005—the investigators determined that Rh-negative status was not higher among the mothers of children with autism. In addition, the mothers of children with autism were not more likely to have been exposed to antepartum Rh immune globulin containing thimerosal, and were not more likely to have an Rh-negative incompatible pregnancy. These findings were also true for autism subtypes.

The authors concluded that the results "support the consensus that exposure to ethylmercury in thimerosal is not the cause of the increased prevalence of autism" (Am. J. Med. Genet. Part A 2007;143A:1397-407).

Therefore, based on the information currently available, it is fair to say there is no compelling evidence indicating that exposure of the developing brain to mercury, either in the fetus or the developing child, is a cause of autism. And as the authors point out, these findings also have implications for other countries, where multidose vials that contain thimerosal continue to be used.

As for other potential prenatal causes of autism, there have been more case reports of autism in children exposed in utero to valproic acid, isotretinoin, or alcohol than one would expect. But I emphasize that these are case reports and merely associations at this point, not proven causes.

Efforts are underway to further investigate the possible association between prenatal exposure to valproic acid and autism. At the Motherisk Program, a teratogen information service at the Hospital for Sick Children in Toronto, we are following the long-term development of children exposed in utero to valproic acid, which we hope will pick up an association with autism, if such a link exists.

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Contraceptive Rod Efficacy In Obese Still Unknown

BY DAMIAN McNAMARA
Miami Bureau

Miami Beach — The advantages and disadvantages of a contraceptive implant have become better known, but there are still no data on its efficacy in overweight or obese women, according to a presentation at an ob.gyn. conference sponsored by the University of Miami.

The Food and Drug Administration cleared Implanon (Organon International) for marketing in July 2006. It is the first single-rod, 68-mg etonogestrel, subdermal implant. The core is 40% ethylene vinyl acetate, which provides a slow, steady release of progestin for up to 3 years, according to clinical trials.

However, overweight and obese women were excluded from the preapproval studies. "This is kind of the kicker—efficacy in overweight women," Dr. Paul M. Norris said. Women who weighed more than 130% of their ideal body weight were not studied. Such an exclusion would be "very impractical" in the United States, Dr. Norris added.

Implanon replaces the six-rod Norplant device, which was removed from the market following reports of product migration and side effects, Dr. Norris said. "The data on Norplant suggested it was still efficacious, although less so, in overweight patients. But I am not sure you can apply this finding to Implanon."

Implanon is inserted in the subepidermal groove of a woman's arm between her biceps and triceps, about 6-8 inches up from the crux of the elbow. Physicians can order Implanon only upon completion of a training program on insertion and removal sponsored by the manufacturer. "They were concerned about injections in other vital structures. So far, the programs have gone well," said Dr. Norris, who is on the obstetrics and gynecology faculty at the University of Miami. He is on the speakers' bureau for Organon.

"The device to insert the implant looks like the Depo-Provera syringe," Dr. Norris said. "The blue placebo injector for practice has a pregnancy rate of about 85%, so make sure you are using the white injector with the active ingredient."

Insertion time is a mean of about 1 minute, compared with 4 minutes for the Norplant, Dr. Norris said. The 4-cm-long, 2-mm-diameter Implanon rod is not radiopaque. "If you lose an implant, you cannot palpate it 3 years later," he said. "It is very easy to pick up on ultrasound, but you need at least a 10-MHz wand, which is not common in most ob.gyn. offices," he said.

Implanon's contraceptive effects are reversible—a woman's fertility quickly returns after removal, according to the manufacturer.

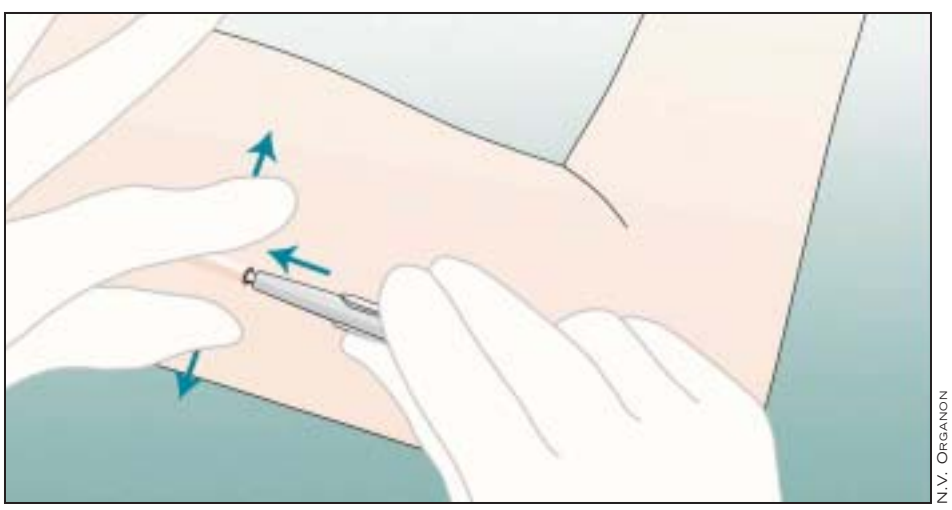
The mean removal time for Implanon is 3 minutes, compared with 11 minutes for Norplant, Dr. Norris said. "This is the mean, and some cases can take almost an hour." In clinical trials, 1% of 923 participants experienced complications at implant insertion and 1.7% had complications at implant removal.

Contraindications include a known or suspected pregnancy. "It likely won't hurt the pregnancy, but it will not prevent a pregnancy if it is already there," Dr. Norris said. History of or current thrombotic disease, history of breast cancer, hepatic tumors, active liver disease, and undiagnosed abnormal genital bleeding are other contraindications.

Bleeding changes were the most common reason women chose to stop Implanon in clinical trials (cited by 11% of participants). Irregular bleeding and spotting is a common side effect, Dr. Norris said. In the studies, patients using Implanon reported an average of 18 days of bleeding or spotting every 90 days. "The problem is this is unpredictable," he said. "With the pill or patch, you have a better idea when to anticipate bleeding or spotting."

Prolonged bleeding occurs in almost 20% of patients, so you will have some patients who are unhappy, Dr. Norris said. "Counsel patients about the unpredictable pattern and frequency of bleeding. If they are okay with it, they should do well."

In terms of contraceptive efficacy, six pregnancies were reported in 20,648 cycles in the clinical trials. These patients were likely to have been already pregnant when they had the implant inserted, Dr. Norris said. "Most seemed to occur soon after the insertion, so it probably had to do with timing. Resist the temptation to put in the Implanon if the patient is midcycle and says she has not had sex for 4 weeks," he said. ■



N.V. Organon

The Implanon contraceptive rod is implanted in the subepidermal groove of the arm between the biceps and triceps, 6-8 inches above the crux of the elbow.