Postmarketing Studies Advised

17P Injection *from page 1*

medical Corp., conduct postmarketing safety studies. Dr. Davidson and other panelists also were concerned about 17P's long-term effects on reproductive development in children exposed to the drug in utero.

"I'd like a registry of all children exposed to this," said Dr. William Steers, a panelist, and chairman of the urology department at the University of Virginia, Charlottesville.

The FDA is not bound by its panels' advice, but usually follows it. The agency granted 17P priority-review status and is due to act by Oct. 20. The drug would be sold by Sunnyvale, Calif.–based Adeza under the brand name Gestiva.

Formerly marketed as Delalutin, 17P was approved by FDA in 1956 for treatment of recurrent miscarriage, threatened miscarriage, postpartum pain, and advanced uterine cancer, but was withdrawn in 1999 due to manufacturing issues. However, since that time, it has been used in a variety of settings, including as a preterm birth preventive, with hospitals compounding 17P.

Preterm birth is a growing problem in the United States, with more than 500,000 tallied by the CDC in 2004, an 18% increase over the 1990 total.

The pivotal study was conducted by the National Institute of Child Health and Human Development and published in the New England Journal of Medicine (2003;348:2379-85). Adeza was given access to the database and packaged it as a new drug submission to the FDA.

Preterm birth is a growing problem in the United States, with more than 500,000 tallied by the Centers for Disease Control and Prevention in 2004, an 18% increase from 1990. The March of Dimes estimated that hospital expenses for preterm or low-birth-weight infants totaled $18 billion in 2003.

In October 2003, the American College of Obstetricians and Gynecologists Committee on Obstetric Practice issued a statement supporting use of 17P, but only in women with documented history of preterm birth before 37 weeks (Obstet. Gynecol. 2003;102:1115-6).

The randomized, placebo-controlled double-blind multicenter study followed 463 women who received weekly intramuscular injections (250 mg/mL) starting from weeks 16-20 of gestation through 36 weeks or birth. The data safety and monitoring board stopped the study early because 17P's effectiveness was statistically significant. According to Adeza, 37% of women given 17P in the intent-to-treat analysis had preterm birth before 37 weeks, compared with 55% of those given a placebo injection.

FDA reviewers, however, took a closer look at the birth rate at less than 35 and less than 32 weeks, saying that they were more accurate predictors of neonatal morbidity and mortality. At less than 35 weeks, 22% of women in the 17P group had given birth, compared with 31% of the placebo group. At less than 32 weeks, 13% of the 17P women had given birth, compared with 20% of the placebo group.

Dr. Barbara Wesley, a medical officer in the FDA's division of reproductive and urologic products, said at the meeting that although the percentages of preterm births in the 17P arms were lower at 35 and 32 weeks, "based on the adjusted 95% confidence interval, the upper limits suggest that 17P may be no better than vehicle." Dr. Wesley also pointed out that a smaller proportion of women in the 17P arms remained pregnant at 24-25 weeks than those in the placebo arm. "The early increase in fetal loss in the 17 hydroxy arm is of concern," she said.

Infants born to women in the 17P group did have statistically significantly less necrotizing enterocolitis, intraventricular hemorrhage, need for supplemental oxygen, and days on respiratory therapy.

Dr. Wesley raised caution flags on the higher incidence of gestational diabetes, preeclampsia, and oligohydramnios in women given 17P.

A follow-up study was conducted in 194 infants in the 17P group and 84 in the placebo group, when they were 30-64 months of age. The children were given the Ages and Stages Questionnaire and physical exams, and parents were surveyed on developmental milestones. Although there appeared to be no difference between the two groups, the findings "should be taken with caution because the number of children is small," said Dr. Wesley.

There was some suggestion of reproductive delay or abnormality at the time of follow-up, with 2% of the 17P group having abnormalities, compared with 1% of the placebo group, according to Adeza. The March of Dimes testified in favor of approval of 17P.

Dr. Nancy Green, medical director of the group, said that based on the data from the New England Journal of Medicine study, and using 2002 data from two state health departments, there were about 30,000 recurrent singleton preterm births in the United States in 2003. If all 30,000 of these women received 17P, about 10,000 preterm births would be avoided. Product labeling should clearly direct use only in preventing recurrent preterm birth and the company should be required to conduct postmarketing studies, said Dr. Green.

Dr. Michael Paidas, director of the program for thrombosis and hemostasis in women's health at Yale–New Haven Hospital, New Haven, Conn., also testified for approval. "The main problem we have right now is that we can't get doctors access to this drug," said Dr. Paidas, who has served as a speaker for the March of Dimes and as a paid speaker for Adeza. ■

Half of Stillbirths Unexplained; Don't Overlook Infection as Cause

BY ALICIA AULT
Associate Editor, Practice Trends

Asheville, N.C. — When looking for causes of stillbirth, obstetricians and pediatricians should not overlook infection, Dr. Sean Blackwell said at the Southern Obstetric and Gynecologic Seminar.

Though the fetal death rate has declined, about half of stillbirths are due to unexplained causes, said Dr. Blackwell of the maternal fetal medicine division at William Beaumont Hospital in Royal Oak, Mich.

A recent paper (Sem. Perinatol. 2006;30:20-3) hypothesized that at least 10% of stillbirths result from infection, a rate equal to the number of deaths caused by fetal anomalies but slightly less than those caused by fetal growth restriction (14%), abruption (14%), or cord- or placenta-related problems (18%). The same study estimated that 27% of stillbirths have unexplained causes.

The number of unexplained stillbirths increases with rising gestational age, said Dr. Blackwell, adding that some of these cases may be undiagnosed or undetected infection.

A variety of pathogens have been associated with stillbirth, including spirochetes, protozoans, viruses, and bacteria, he said. There are three potential ways a fetus can acquire an infection: through systemic maternal illness; through the cervicovaginal compartment; or via a transplacental route. Maternal illness may result in a proinflammatory response that redistributes blood flow, leading to uteroplacental insufficiency.

An ascending infection will infect fetal and placental tissue, leading to sepsis. Group B streptococci, *Escherichia coli*, *Ureaplasma,* and *Candida* are known to use the ascending route, said Dr. Blackwell.

Similarly, a pathogen that crosses the placental barrier will infect fetal and placental tissue, leading to sepsis and anomalies. Malaria, syphilis, coxsackievirus, cytomegalovirus, and parvovirus are known to cross the placenta.

Dr. Blackwell said that several papers have shown that parvovirus may lead to fetal death by previously unknown mechanisms. In testing tissue from stillbirths with unexplained causes, Dr. Blackwell and colleagues found that though 43 of the 44 had negative cultures, there were changes in the tissue consistent with exposure to an infectious agent (J. Matern. Fetal Neonatal Med. 2003;14:151-7 and 241-6).

Recent findings show that genetics may also play a role in susceptibility to stillbirth. Some women have a polymorphism that appears to cause hyperresponsiveness to infections like bacterial vaginosis, resulting in a proinflammatory cascade that could harm the fetus. There is growing evidence also that fetal response to infection may be partly governed by phenotypes. Several papers have postulated that there may be a normal response in which the fetal immune response results in the triggering of labor, which helps the fetus escape a hostile environment, Dr. Blackwell said. He urged clinicians to conduct full work-ups on stillbirths, including taking cultures of the placenta and blood and organs of the fetus in order to get some answers. ■

Antiangiogenic Protein Under Study As Promising Preeclampsia Marker

Chicago — Measures of soluble fms-like tyrosine kinase 1 (sFlt-1), a circulating antiangiogenic protein secreted in excess by the placentas of women with preeclampsia, may prove to be a screening test for preeclampsia.

"Looking to the future, I have a lot of faith in blocking sFlt-1" as a possible treatment for preeclampsia, Dr. Sharon Maynard said in an interview after her presentation at a meeting on clinical nephrology sponsored by the National Kidney Foundation. The first phase I trial of an agent that blocks sFlt-1 will begin next year. If shown to be safe and effective, a potential treatment could be available within 3-4 years.

The ability to prevent and treat preeclampsia has long eluded medicine, said Dr. Maynard, a nephrologist at George Washington University. Most studies have addressed preventive therapies for preeclampsia: calcium, antioxidants, aspirin, magnesium, and blood pressure control.

Several small studies initially suggested that calcium supplementation could help prevent preeclampsia, but the findings did not hold up in later studies. Outcomes were comparable in one large trial that randomized more than 4,500 healthy nulliparous women to calcium or placebo (N. Engl. J. Med.1997; 337:69-76). A subgroup analysis of these data indicated women with low baseline calcium levels may derive some benefit from supplements. A World Health Organization–sponsored trial of 5,000 women with low baseline calcium levels also revealed a lower risk of preeclampsia and neonatal death.

Antioxidants similarly failed to hold up to the rigors of a controlled trial in 2,395 women. In fact, the gravid women taking antioxidant supplements had a greater risk of low-birth-weight babies and stillbirths.

The data on aspirin in this population are "the most confusing of all," noted Dr. Maynard. Although three large randomized controlled trials of 12,000 high-risk women found no differences with aspirin versus placebo, results were mixed in a subsequent metaanalysis of 51 trials involving 36,500 women. A Cochrane analysis showed that benefits were seen in small studies, but not in large ones. "I am really concerned that there may be no benefit at all," she said.

Although magnesium has not been shown to prevent preeclampsia, it should be used "across the board. [It] clearly cuts the risk of seizures in half," said Dr. Maynard.

—Sarah Pressman Lovinger