# One-Course Antenatal Steroids Reaffirmed

BY PATRICE WENDLING
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DALLAS — Multiple courses of antenatal corticosteroids did not offer additional benefits to infants born to mothers at high risk of preterm delivery, and were associated with significantly smaller birth weight, birth length, and head circumference in a phase IV study of 1,858 women.

In 2000, the National Institutes of Health reaffirmed that a single course of antenatal corticosteroids should be considered for pregnant women between 24 and 34 weeks of gestation who are at risk for preterm delivery within 7 days, but concluded that the data available at that time were inadequate to argue for or against repeat or rescue courses of antenatal corticosteroids (ACS) for fetal maturation.

Treatment consists of two doses of 12 mg betamethasone given intramuscularly 24 hours apart or four doses of 6 mg betamethasone given intramuscularly 12 hours apart.

In their latest October 2007 Guidelines for Perinatal Care, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics advise that "repeated corticosteroid courses should not be used routinely because clinical trials show decreased brain size, decreased birth weight, and adrenal insufficiency in neonates exposed to repeated doses."

In the current study, the primary composite outcome of mortality, severe respiratory distress syndrome, grade 3-4 intraventricular hemorrhage, periventricular leukomalacia, bronchopulmonary dysplasia, or necrotizing enterocolitis was similar between infants born to women who received multiple courses of corticosteroids (12.9%) and those born to women receiving placebo (12.5%) after an initial course of corticosteroids. The odds ratio was 1.04.

The rate of still births also was not significantly different between groups (43 vs. 40, OR 1.08), principal investigator Dr. Kellie Murphy reported on behalf of the Women in the Multiple Courses of Antenatal Corticosteroids or Preterm Birth Study (MACS) group at the annual meeting of the Society for Maternal-Fetal Medicine.

The interventional study was conducted at 80 centers and included women at 26-30 weeks of gestation who remained at high risk for early delivery 14 or more days after being given a single course of ACS. At randomization, 937 received two doses of 12 mg betamethasone intramuscularly 24 hours apart every 14 days until 33 6/7 weeks or delivery and 921 received placebo. The mean age in both groups was 29 years.

The 1,164 babies born to women in the repeat-corticosteroid group weighed less (2,216 g vs. 2,330 g), were shorter (44.5 cm vs. 45.4 cm), and had a smaller head circumference (31.1 cm vs. 31.7 cm), compared with the 1,140 babies born to mothers in the placebo group. All the differences were statistically significant.

**The 1,164 babies born to women in the repeat-corticosteroid group weighed less, were shorter, and had a smaller head circumference vs. the placebo group.**

"What was surprising to us is that even though the majority of patients, 70%, received only one or two [additional] doses, which one wouldn't think was a large amount, there was still a significant decrease in all those parameters," said Dr. Murphy, a perinatologist at Mount Sinai Hospital, Toronto.

In all, 385 women received one additional course, 305 received two additional courses, and 247 received three to five courses.

An unplanned ad hoc analysis of infants born less than 7 days after study drug exposure and those born less at than 32 weeks' gestational age showed no significant difference in the primary composite outcome between groups.

Dr. Murphy acknowledged during the question-and-answer session that the MACS findings are quite different from those of the recent Australian ACTORDS study in which repeat doses of antenatal steroids reduced neonatal morbidity without changes in body size or survival free of neurosensory disability at 2 years (N. Engl. J. Med. 2007;357:1179-89).

That study used a single intramuscular injection of betamethasone 11.4 mg repeated weekly, not times two; the definition of respiratory distress syndrome was slightly different; and *z*-scores were used to determine outcomes—all of which may account for the different findings, she said.

The MACS group concluded that multiple courses of ACS should not be given every 14 days to women at increased risk of preterm birth after receiving an initial course. When asked by an audience member about the efficacy of a single course of ACS, Dr. Murphy replied, "I still believe that it is efficacious and beneficial."

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## Drugs, Pregnancy, And Lactation

# Patient Perception of Teratogenic Risk

BY GIDEON KOREN, M.D.

Since the thalidomide disaster, people have feared the teratogenic effects of medications and many pregnant women believe that almost any drug is teratogenic.

The way in which women and their families perceive the teratogenic risks of medications—even those with no such risks known—can result in unnecessary anxiety, which in some cases compels them to choose to terminate an otherwise wanted pregnancy.

But when women are provided with the available evidence and accurate information, unfounded fears about drugs that are not considered teratogenic can be put into the proper perspective, particularly today, as more information about the reproductive safety of drugs is becoming available.

A striking example of the impact an exaggerated perception of risk can have is provided by a 1987 report from Greece, which estimated that in May 1986, the month after the Chernobyl nuclear accident in Ukraine, 23% of early pregnancies in Athens were terminated because of a perceived radiation risk (Br. Med. J. [Clin. Res. Ed.] 1987;295:1100).

When we started the Motherisk program, a teratogen information service, in 1985, our primary focus was to prevent malformations in cases where women were exposed to genuine teratogens.

But it soon became apparent that our work would also include preventing unnecessary terminations of pregnancies.

We received many calls from pregnant women who had been exposed to nonteratogenic drugs in early pregnancy who were concerned that the risk of having a baby with a malformation was huge. They were considering terminating their pregnancies. Today, we continue to receive such calls, including some from women whose physicians have advised them to terminate pregnancy because of such an exposure.

Because of this experience, we have conducted studies for more than 20 years on how women perceive the teratogenic risk of medications and other exposures, such as dental x-rays, and we have documented that providing them with the available, accurate information has a significant impact on their misperceptions, swaying them away from choosing to terminate the pregnancy.

In our first study of 80 women who consulted Motherisk about drug, chemical, and radiation exposures, we used a visual analogue scale measuring a woman's perception of risk during pregnancy, with a range of 0%-100%.

We were surprised to find that women exposed to nonteratogenic drugs such as acetaminophen, or to dental x-rays, which have no known fetal risk, considered themselves to be at about a 24% risk of having a major malformation, similar to the magnitude of risk associated with thalidomide. But after the women were provided with relevant information, this percentage dropped to about 14.5%, and there was a significant reduction in the tendency toward choosing to terminate the pregnancy (Am. J. Obstet. Gynecol. 1989;160:1190-4).

Since that time, we have conducted similar studies on the perceptions of risk associated with other exposures, including mild maternal drinking, x-rays, recreational cocaine use, and treatments for nausea and vomiting, with similar results. In a 1999 study, we found that evidence-based counseling of women with unfounded fears of the teratogenic risks of drug treatment for nausea and vomiting reduced the proportion of women in the study who mistakenly believed that antiemetic drug therapy increased the risk of major malformations (Reprod. Toxicol 1999;13:313-9).

Radiation exposure elicits huge anxieties, as does mild alcohol consumption and use of drugs that are teratogenic at high doses in animals, but has not been shown to be teratogenic in humans.

Because of the fear of fetal-alcohol syndrome, some women consider terminating pregnancy because of a few drinks they had before they knew they were pregnant—yet another example where misinformation and misperception unnecessarily lead to terminations of otherwise wanted pregnancies.

The lack of information in the product labeling of drugs contributes dramatically to these misperceptions of risk. The current pregnancy category letter labeling system in the United States remains unchanged, despite plans to revise the system.

Although more information about safety during pregnancy has been added to some drug labels, in most cases, labels suggest there are not enough data—even if relevant data exist. A physician who reads the fluoxetine label, for example, may not find adequate information to counsel a patient, despite evidence in the literature that the drug is safe in terms of morphology, as well as IQ and learning.

By providing evidence-based counseling, clinicians can address a patient's unrealistically high perception of risk and make a difference. Clinicians can obtain more information about the reproductive risks of drugs from the Organization of Teratology Information Specialists (866-626-6847 or www.otispregnancy.org). Other resources include Motherisk (www.motherisk.org), and the MGH Center for Women's Mental Health (www.womensmentalhealth.org). There is also my book, "Medication Safety in Pregnancy and Breastfeeding" (McGraw-Hill, 2007), which summarizes information from the Motherisk database.

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Pages 12a—12b◊