Expert: Repeat Steroids Can Be Justified in Certain Cases

BY SHERRY BOSCHERT
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SAN FRANCISCO — Three randomized, controlled trials now show evidence of beneficial effects from a limited number of repeat courses of prenatal corticosteroids for fetuses at risk of preterm delivery, according to Julian T. Parer, M.D.

Those aren't necessarily the official conclusions of the studies, however, he acknowledged at a meeting on antepartum and intrapartum management sponsored by the University of California, San Francisco.

Two of the three studies found no overall benefit from repeat prenatal steroids but reported significantly less respiratory distress and morbidity in babies born at younger gestational ages if they got more than one course of betamethasone prenatally.

The third study showed a benefit from repeat prenatal steroids, but the investigators will not draw conclusions about the results until after a 2-year follow-up period, said Dr. Parer, who is professor of ob.gyn. at the university.

Dr. Parer said he has no financial relationships with companies that make corticosteroids.

A consensus statement issued in 2000 by the National Institutes of Health says that repeat courses of corticosteroids should not be used routinely due to insufficient data from randomized clinical trials.

Data from these three more recent studies, however, support the administration of more than one course of prenatal corticosteroids for women who are at at high risk of delivering before 28 weeks, Dr. Parer said.

"It is possible to justify repeating at least a single course in those patients, particularly if given at a 2-week interval," he said.

Dr. Parer relayed results of the third, and most recent, study that he heard presented at a conference in Australia earlier this year. That study included 982 pregnant women at risk for preterm delivery who had received one course of prenatal corticosteroids.

The women were randomized to weekly corticosteroids or placebo; treatment continued until 32 weeks' gestation only if the risk for preterm delivery continued.

The study included singletons, twins, and triplets for a total of 1,100 fetuses that were a mean of 28 weeks' gestation at enrollment. The risk factors for preterm birth were similar between groups.

Results showed significantly lower rates of respiratory distress syndrome (RDS) and severe RDS in the weekly corticosteroid group. With weekly corticosteroids, 33% developed RDS, and 12% had severe RDS, compared with 41% and 20%, respectively, in the placebo group.

The need for oxygen or mechanical ventilation fell less dramatically in the weekly corticosteroids group, compared with placebo, but it was not clear whether these differences were significant.

There were no significant differences between groups in the need for intensive care, duration of intensive care, rates of chronic lung disease or severe intraventricular hemorrhage, or maternal outcomes.

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DR. PARER

Although birth weights were somewhat lower in the steroid group, the weight differences between groups resolved by the time of hospital discharge, he said. Average neonatal length and head circumference did not differ between groups.

No harmful effects of repeat corticosteroids were noted. Of those women who received repeat courses, 24% received at least four courses. The investigators declined to present a conclusion until they've completed 2 years of neurodevelopmental follow-up, he said at the meeting.

A separate study, which was reported at the Society of Maternal and Fetal Medicine meeting in 2004, randomized 495 women after an initial course of prenatal corticosteroids to weekly courses or placebo.

The study was stopped prematurely at 23% of its expected enrollment due to concerns about birth weights, and no signs of a substantial reduction in overall morbidity in the steroid group.

The investigators concluded that there was no benefit to repeated courses of corticosteroids, but Dr. Parer highlighted the "much more impressive" results in infants delivered at less than 32 weeks. These babies had significantly less bronchopulmonary dysplasia and less need for mechanical ventilation or continuous positive airway pressure if they had received repeat corticosteroids, he noted. Birth weights were lower only in infants who had been exposed to more than four courses of corticosteroids.

A third study that randomized 502 women to a single course or weekly courses of corticosteroids also was stopped early and reported no benefit from weekly prenatal steroids (JAMA 2001;286:1581-7).

That study also reported a significantly lower incidence of RDS in babies born before 28 weeks whose mothers received repeated courses of corticosteroids, Dr. Parer noted.

Critics contend that both of these studies were too small and too short to detect significant differences in their primary end point of composite morbidity. ■

DRUGS, PREGNANCY, AND LACTATION

Antihyperlipidemic Agents

The antihyperlipidemic class of drugs can be subdivided into bile acid sequestrants, HMG-CoA reductase inhibitors, fibric acid derivatives, ezetimibe, and niacin. With the possible exception of familial hypercholesterolemia, there appears to be no maternal benefit for treating hyperlipidemia in gestation. Nearly all reported pregnancy exposures have occurred accidentally. If treatment is required, only bile acid sequestrants are considered compatible in pregnancy and lactation.

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Ezetimibe (Zetia) appears to be low risk in gestation, but not in lactation.

Because most drug-induced adverse effects in nursing infants have been reported during the first month after birth, delaying treatment of a nursing mother until after this period appears to be the best course.

Cholesterol is the precursor of bile acids that are excreted from the liver and gallbladder into the intestine to aid in the digestion of fat. Bile acid sequestrants—cholestyramine (Questran and various other names), colestipol (Colestid), and colesevelam (WelChol)—are anion exchange resins that form insoluble complexes with bile acids in the intestine. The complexes are then excreted in the feces, removing cholesterol from the system.

Cholestyramine has been used as a treatment for intrahepatic cholestasis of pregnancy and as an antidote for some types of diarrhea, chlordecone pesticide poisoning, and digitalis toxicity. Because bile acid sequestrants are not absorbed into the systemic circulation, they do not represent a direct risk to the embryo or fetus and are considered compatible with pregnancy (all are rated risk factor B) and lactation. However, the resins also bind fat-soluble vitamins (vitamins A, D, E, and K) in the gut, and deficiencies of these vitamins may result.

The six HMG-CoA reductase inhibitors (statins) are atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor, Altocor), pravastatin (Pravachol), rosuvastatin (Crestor), and simvastatin (Zocor). All are contraindicated in pregnancy (risk factor X). Case reports and surveillance studies have described healthy outcomes from a number of pregnancies inadvertently exposed in the first trimester and later. The largest number of cases (187) were reported with simvastatin, with 86 cases that could be evaluated: 74% had normal outcomes, 15% resulted in spontaneous abortion, 6% of cases demonstrated with congenital anomalies, 4% of cases had effects related to prematurity, and 1% resulted in fetal death. Three of the five birth defect cases were not related to simvastatin because of the timing of exposure or the outcome was a known chromosome defect. The remaining two cases involved unilateral cleft lip and a clubfoot, neither of which appear to be attributable to simvastatin.

A 2004 reference described 178 cases of first-trimester exposure to statins reported to the Food and Drug Administration. Among the 52 cases suitable for evaluation, there were 20 major malformations, some thought to be consistent with inhibition of cholesterol biosynthesis. All defects involved a lipophilic statin (atorvastatin, cerivastatin [Baycol], lovastatin, or simvastatin). No defects were reported with pravastatin, a hydrophilic agent with low tissue penetration that is not associated with animal developmental toxicity. Because all statins are probably excreted into milk, women taking these drugs should not breast-feed.

Among fibric acid derivatives, only gemfibrozil (Lopid) has some human data. The other agent, fenofibrate (TriCor), has no human data. The animal data (developmental toxicity in two animal species at doses up to 10 times the human dose) for each drug suggest there may be a risk to the human embryo or fetus. The safest course is to avoid these drugs in pregnancy (both are risk factor C). Although there are no data, the drugs are probably excreted into milk, and women on these agents should not breast-feed.

Ezetimibe (risk factor C) selectively inhibits the intestinal absorption of cholesterol and related phytosterols. At doses up to 10 times the human dose, the drug is teratogenic in rats but not in rabbits. Human pregnancy exposures have not been reported. If therapy during pregnancy is mandated, ezetimibe appears to be a better choice than statins. There are no data on use during lactation, but the drug is probably excreted into milk. Nursing infants should be monitored for headache, diarrhea, arthralgia, pharyngitis, sinusitis, and other adverse effects observed in adults.

Niacin (nicotinic acid) is converted in vivo to niacinamide, the active form of vitamin B_3. But high doses (up to 2,000 mg/day) used for hyperlipidemia have not been studied in pregnancy. Because niacinamide is actively transported to the fetus, producing higher concentrations in the fetus and newborn than in the mother, niacin is best avoided during pregnancy and lactation.

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