Inflammatory Markers Not Tied to Epidurals

BY SUSAN BIRK
Contributing Writer

CHICAGO — Proinflammatory cytokine levels escalate with normal labor but are not an underlying mechanism of epidural-related fever, according to the results of a study of 92 term parturients.

The researchers found no differences between febrile and afebrile patients in serum levels of the proinflammatory cytokine interleukin-6 during labor or post partum, Dr. Venkat Mantha reported at the annual meeting of the Society for Obstetric Anesthesia and Perinatology.

Dr. Mantha of the University of Pittsburgh's Magee Women's Hospital and associates mapped changes in interleukin-6 levels at 4-hour intervals during labor and after delivery and measured neonatal interleukin-6 levels in umbilical cord blood samples in 92 healthy, nulliparous term parturients who went into spontaneous labor and who all received epidural analgesia.

The generally accepted view is that epidural-related fever has a physiological basis and is the product of changes in thermoregulatory mechanisms.

Interleukin-6 levels rose significantly during labor in women who did not have fever as well as in those who did, he said.

The researchers drew peripheral blood and took tympanic temperatures at the time of labor epidural placement and every 4 hours until 4 hours following delivery.

Patients who, at any of the intervals, had a temperature equal to or greater than 38° C were considered febrile.

After delivery of the placenta, umbilical cord blood samples were taken, and neonatal rectal temperatures were taken within 30 minutes of birth.

The 66 afebrile patients and 26 febrile patients shared common characteristics with respect to height, weight, gestational age, and age.

In both groups, interleukin-6 was significantly higher at 8 hours and following delivery, compared with the baseline measurement, but no significant differences were found between the two groups in interleukin-6 levels at any of the measurement intervals.

In addition, while the neonates of febrile mothers had significantly higher temperatures than those of afebrile mothers (36.97° C and 36.68° C, respectively), their umbilical cord serum interleukin-6 levels were statistically the same as the afebrile group.

"We did not find any inflammatory basis for epidural-related fever," said Dr. Mantha. "We agree with reports that suggest that maternal serum interleukin-6 levels rise in response to labor."

The study reaffirms the generally accepted view regarding the nature of epidural-related fever, Dr. Mantha commented.

This thinking holds that epidural-related fever is the product of changes in thermoregulatory mechanisms, and that increases in proinflammatory cytokines such as interleukin-6 occur in normal pregnancy and labor.

"All of these years, it's been accepted that epidural-related fever has a physiological basis and that interleukin-6 plays a role in normal labor," Dr. Mantha said in an interview, noting that interleukin-6's role in labor is not yet understood.

However, studies showing an increase in interleukin-6 during normal labor did not differentiate between patients who had received epidural analgesia and those who had not, he said.

"This [current study] was the first study where the primary aim was to try and find whether there is a relationship between epidural fever and increases in serum levels of interleukin-6," Dr. Mantha said.

A catalyst for this investigation was the publication of two studies that challenged the thermoregulatory view of epidural-related fever by showing a strong relationship between epidural-related fever and increases in interleukin-6, suggesting the possibility that the fever has an inflammatory basis (Am. J. Obstet. Gynecol. 2002;187:834-8; Am. J. Obstet. Gynecol. 2003;188:269-74).

Dr. Mantha noted that the study was limited by the fact that it did not include women who had not received labor epidural analgesia; however, performing a randomized study including these women is difficult because more than 90% of parturients at Magee request labor epidural analgesia. ■

Drugs, Pregnancy, And Lactation

FDA to Revise Pregnancy Category Labeling

BY LEE COHEN, M.D.

The Food and Drug Administration has proposed revisions to the longstanding system of pregnancy category labeling for all medications.

The current system has classified the reproductive safety of medications across five risk categories—A, B, C, D, and X—usually based on available data when a drug is approved.

The proposed system will eliminate the letter categories and instead will include sections on pregnancy and lactation, each with information summarizing risks, clinical considerations, and available human and animal data.

The implications of the proposed system with respect to psychiatric medications are significant.

In previous columns, I have discussed some of the limitations of the category label system for various psychiatric medications.

There are examples of medications with a sparse amount of reproductive safety information that does not indicate an adverse effect, which bear a more favorable category label than other medicines for which very extensive reproductive safety are available, but perhaps where animal safety data suggest some cause for concern.

There are also examples where evidence of adverse reproductive effects in animals dosed with toxic amounts of a medicine can trump significant amounts of human data supporting reproductive safety.

A dramatic example of the current system's limitations is lithium, a category D drug because of clear evidence of Ebstein's anomaly associated with first-trimester exposure. Yet the absolute risk of the cardiac anomaly is only 0.05% following first-trimester exposure.

Considering the high rate of relapse of bipolar disorder associated with stopping lithium before or during pregnancy, this may be a risk many patients are willing to take, in collaboration with their psychiatrists.

The current system also does not distinguish between relative amounts of data, and typically lumps a class of medications into one category, instead of considering the drugs as individual molecules.

All the selective serotonin reuptake inhibitors are labeled category C, yet the amount of reproductive safety data available for the individual SSRIs is highly variable.

Moreover, information in the letter category system has been limited to reproductive safety during the first trimester and does not address some of the potential risks of exposure during the second and third trimesters, and peripartum period.

Part of the problem is that with few exceptions, industry has failed to embrace a global product safety initiative regarding establishing registries for these products in a systematic way shortly after a drug is marketed.

In May, almost a decade after indicating that the pregnancy and lactation labeling system would be changed, the FDA announced the proposed changes, which address these limitations.

The pregnancy section would include a fetal risk summary, which would describe the risks to the fetus associated with exposure to the medicine based on available data; and clinical considerations, which would include information about the effects of the drug if a woman takes it before she knows she is pregnant and the risks of the disease for the mother and baby.

A third section would summarize the available human and animal data that provide the basis of the fetal risk summary. The labor and delivery section in the current drug label would be eliminated, with this information included in the pregnancy section. The section on lactation would include the same sections on risk summary, clinical considerations, and data.

The clinical implications of dropping the letter category system are considerable. These categories have frequently been used to switch patients from one medicine to another somewhat arbitrarily.

Even well-intentioned clinicians have switched a patient to a medicine based on the category label, when there are less available reproductive safety data in humans, but perhaps animal data were of some concern.

For example, a patient who is exquisitely responsive to a category C drug may have been switched to a category B drug during pregnancy even though there are very sparse data for the drug with the category B rating, but none of it adverse.

Once the new system is in place, this type of arbitrary change in a patient's medication based on the category label will hopefully cease. Moving from a categorical system of classification to a system that is more inclusive of available reproductive safety information should help clinicians rather than confuse them.

Clinicians will be provided with more information in a drug's label that actually describes results of studies and will be able to see firsthand the type of information that is available and the quality of data, as well as references to studies.

As a result, we will be provided with a more global risk assessment across pregnancy, including the peripartum period and lactation.

Regardless of the system used, the process of making decisions about the use of any medicine, particularly psychotropics, during pregnancy should be made on a case-by-case basis, weighing the varying amounts of information on the medicine and the patient's underlying disease state.

Many clinicians might believe that more information will provide an opportunity to thread the clinical needle associated with the risk-benefit decision in a more precise fashion.

This may not always be the case but at least we can come that much closer to refining the risk-benefit decision for patients who need to make these types of clinical decisions with their doctors.

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