Study Looks at Oxygen Saturation in Preemies

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FROM THE NEW ENGLAND JOURNAL OF MEDICINE

Hypertensive disorders of pregnancy (complicate 5%-10% of pregnancies and are a leading cause of maternal and perinatal mortality and morbidity. Treatment with antihypertensive medications is intended to prevent adverse maternal and infant outcomes. However, there is no clear consensus regarding the benefit of treatment for mild to moderate gestational hypertension. The maternal/fetal risks of no treatment, such as possible progression to severe hypertension and its associated complications, have not been shown to clearly outweigh the fetal risks of treatment with antihypertensive medications, which may include intrauterine growth restriction and other neonatal complications.

A recent study published online in May in the BJOG: An International Journal of Obstetrics & Gynaecology suggests that the decision to treat mild to moderate hypertension should include concomitant consideration of long-term neurobehavioral consequences for the child (BJOG 2010; doi: 10.1111/j.1471-0528.2010.02568.x). In an hypothesis-generating historical cohort study conducted in the Netherlands, the authors identified 202 singleton children born in 1 of 12 hospitals between 1983 and 1987, whose mothers had developed pregnancy-induced or pregnancy-aggravated hypertension and were treated with either methyldopa (61), labetalol (38), or bed rest (83). The children underwent a battery of tests to measure IQ, gross motor development, fine motor development, and memory between approximately ages 4 and 9 years. In addition, parents and teachers were asked to evaluate the child’s behavior.

Mean scores on most areas of functional development did not differ significantly between the groups. However, children prenatally exposed to labetalol were about four times more likely to exhibit characteristics of ADHD than were children in the bed rest group based on a standardized Dutch version of the Teacher Report Form (OR 4.1). Children in the labetalol group were also more likely to exhibit these behaviors than were children in the methylxypa group but not significantly so (OR 2.3). Odds ratios for methylxypa existed as an exploratory finding because of the small number of children in each group who were classified as ADHD. The authors suggest that there is biological plausibility for the effect of prenatal exposure to labetalol on subsequent attention and hyperactivity in prenatal exposure to labetalol, and that this effect could be mediated by drug-induced fetal growth restriction and neonatal beta blockade.

This interesting study illustrates two critically important points: The first is the difficulty of conducting observational studies of prenatal medication exposure and long-term neurobehavioral outcomes, and the second is the importance of doing these studies in the first place. With respect to the former, even under the best of circumstances, without a randomized controlled trial it is very difficult to account for differences inherent in the three groups in the Dutch study. These include differences between groups in maternal overweight or obesity, tobacco use, preterm or very preterm delivery, infants born small for gestational age, maternal stress, other drug use, etc., all of which may contribute to risk for ADHD. Severity of the underlying maternal condition as measured by highest diastolic blood pressure, as well as gestational age at which treatment was initiated, varied by group.

Furthermore, differences in age at which the child was tested could have influenced the prevalence of ADHD-like symptoms that were likely to be identified by teacher report. And finally, the study was conducted during a period when standards of clinical practice were in transition in terms of which medication the obstetrician chose to use for treatment, if any. This common occurrence can lead to “channeling” of patients with certain characteristics to time treatment with one of the other drugs, which can carry with it inherent underlying differences in patients that are potentially confounding with respect to the outcome.

Nevertheless, these kinds of studies need to be done. Just as there is a need for systematic postmarketing studies for drug safety with respect to risk for birth defects, there is an equally important need for systematic surveillance for neurobehavioral outcomes. Improved efforts are needed to carefully match groups on key maternal and child characteristics and to address the growing number of potential environmental factors that accumulate the longer the period of time to follow-up developmental assessment. Study designs that involve sufficient sample size to generate enough power to evaluate the outcomes of interest, although difficult to come by, are needed.

All of these issues call for a systematic coordinated approach to evaluating long-term functional outcomes following prenatal drug exposure, which in the end may have the most potential public health importance.

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