DRUGS, PREGNANCY, AND LACTATION

Hypertensive Disorders of Pregnancy

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.

BY CHRISTINA CHAMBERS, PH.D., M.P.H.

The maternal/fetal risks of no treatment, such as possible progression to severe hypertension and its associated consequences, 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 on-line in May in the BJOG: An International Journal of Obstetrics & Gynaecology suggests that the decision to treat mild to moderate hypertension should include consideration of possible long-term neurobehavioral consequences for the child (BJOG 2010 [doi: 10.1111/j.1471-0528.2010.02568.x]). In a 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 (58), 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.

Overall, 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 attention-deficit/hyperactivity disorder than were children in the bed rest group, based on a standardized Dutch version of the Teacher Report Form (odds ratio, 4.1). Children in the labetalol group were also more likely to exhibit these behaviors than were children in the methyldopa group but not significantly so (OR, 2.3). Odds ratios were not adjusted for other factors 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 primary school children, 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 in 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 in time 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 treatment with one or the other drug, 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 comparison 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 exposures, which in the end may have the most potential public health importance. ■

DR. CHAMBERS *is associate professor of pediatrics and family and preventive medicine at the University of California, San Diego. She is director of the California Teratogen Information Service and Clinical Research Program. Dr. Chambers is a past president of the Organization of Teratology Information Specialists (www.otispregnancy.org) and past president of the Teratology Society. She had no conflicts to disclose related to the topic of this column. To comment, e-mail her at obnews@elsevier.com.*

Menstrual Phase Key in Measuring CV Risk in Young Women

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE SOCIETY FOR PEDIATRIC AND PERINATAL EPIDEMIOLOGIC RESEARCH

SEATTLE — Careful timing in measuring high-sensitivity C-reactive protein during the menstrual cycle can make all the difference in classifying young women's risk of cardiovascular disease, new data show.

In a study of 259 healthy premenopausal women, high-sensitivity C-reactive protein (hs-CRP) levels fluctuated considerably over the course of the menstrual cycle, with the highest (and most variable) levels seen during menses and the lowest seen at ovulation.

The proportion of women classified as having a high or moderate risk for cardiovascular disease based on their levels of hs-CRP, a marker of chronic inflammation, was significantly greater when levels measured during menses were used (41%) than when levels at ovulation were used (29%).

"The take-home message here is that the measurement of CRP in clinical settings and in future research studies should be standardized to the menstrual cycle phase," said lead investigator Audrey J. Gaskins, a postbaccalaureate fellow at the National Institute of Child Health and Human Development in Rockville, Md.

"Ideally, [one should] measure CRP around ovulation, when levels are lowest, but that is generally hard to time," she commented. "So I would say any time other than menses, would be ideal."

Several lines of evidence suggest that estrogen may modulate inflammation to a clinically relevant extent when it comes to cardiovascular outcomes, according to Ms. Gaskins.

"The risk of coronary events rises in women after menopause, and this corresponds to when endogenous estrogen levels decrease," she explained. "Also, two recent studies have shown that in regularly menstruating women, there are more acute coronary events in the early follicular phase, when estrogen levels are lowest."

Ms. Gaskins and her colleagues analyzed data from 259 healthy, normally menstruating women, aged an average of 27 years, and who were followed for up to two menstrual cycles in the BioCycle Study.

Some 41% of the women had hs-CRP levels during menses in in the high- or moderate-risk category, whereas only 29% had high levels at ovulation, a significant difference.

Serum samples collected at eight distinct time points during the menstrual cycle were assayed for levels of hormones and hs-CRP. Any hs-CRP values exceeding 10 mg/L were excluded under the assumption that they reflected acute illness.

Ms. Gaskins noted that the population was more diverse than those in previous studies. Some 59% of the women were white, 20% were black, and 21% were of other races. Although 61% had a body mass index in the normal range, 25% were overweight, 10% obese, and 3% underweight (percentages rounded). Seventy four percent were nulliparous, and 4% were smokers.

Study results showed that hs-CRP levels varied widely over the menstrual cycle, she reported. They were highest and also showed the greatest inter-individual variability during menses, and lowest at ovulation, with about a 1.6-fold difference in values between these two time points.

In adjusted models, hs-CRP was significantly associated both with estradiol across the menstrual cycle and with progesterone during the luteal phase. Specifically, hs-CRP levels fell by 24% with each 10-fold increase in estradiol level and increased by 19% with each 10-fold increase in luteal progesterone level.

In a final analysis, the investigators classified the women according to the American Heart Association risk classification system, whereby cardiovascular disease risk is considered high if hs-CRP level is greater than 3 mg/L and moderate if it is 1-3 mg/L.

Although 32% of women had hs-CRP levels in the high-risk category at at least one time point during the menstrual cycle, only 2% consistently had levels in this category at all eight time points.

Some 41% of the women had hs-CRP levels that placed them in the high- or moderate-risk category during menses, whereas only 29% had high levels at ovulation, a significant difference. The percentages at all other time points, except for the midluteal time point, were also significantly lower than those at menses.

Ms. Gaskins said she had no conflicts of interest. ■