Endocrine Disruptors Top Priority for Research

BY JEFF EVANS

WASHINGTON — The potential health threat of environmental exposure to endocrine-disrupting chemicals such as bisphenol A has become a top concern of the Endocrine Society, which issued its first scientific statement on the substances last month.

"There was no question about whether to prioritize endocrine-disrupting compounds as a No. 1 issue to explore above many other issues that were competing that have major public health implications," Dr. Robert M. Carey, president of the Endocrine Society, said at a press briefing at the society's annual meeting. "Science has taken us up to a point where we are concerned."

Researchers also presented animal studies of the possible effects of bisphenol A (BPA) on cardiac arrhythmias and epigenetic imprinting during gestation, as well as the possible continual exposure of most of the U.S. population to levels of the substance at 20 times the Environmental Protection Agency's accepted safe daily intake (50 mcg/kg).

The scientific statement is the "consensus of the best scientists in the world" in summarizing evidence on the effects of endocrine-disrupting chemicals (EDCs) and in identifying basic and clinical research knowledge gaps. "Obviously we don't know all the answers—far from it—for EDCs, so this is extremely important," said Dr. Carey, noting that the EPA announced in April that it will require pesticide manufacturers to test 67 chemicals in their products to determine whether they disrupt the endocrine system.

"We present evidence that endocrine disruptors do have effects on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid disease, metabolism and obesity, and … cardiovascular endocrinology," Dr. Carey said.

EDCs noted in the review include environmental estrogens, or estrogen mimics, most notably BPA—a synthetic monomer that is used in the production of polycarbonate plastics and epoxy resins—as well as polychlorinated biphenyls, diethylstilbestrol, dioxins, and phthalates. Other EDCs identified in the report include antiandrogen substances such as the fungicide vinclozolin and the insecticide DDT and its metabolic derivative DDE (Endocr. Rev. 2009;30:293-342).

'There was no question about whether to prioritize endocrine-disrupting compounds as a No. 1 issue to explore. ... Science has taken us up to a point where we are concerned.'

In light of the findings highlighted in the review, the authors advised several courses of action to address in clinical practice. Clinicians should become educated about the sources and effects of environmental contaminant exposures in utero and across the life span, and should take a careful history of the onset of reproductive disorders along with an occupational and environmental exposure history, according to the statement. Clinicians also can advise patients about minimizing their risks of exposure.

Dr. Hugh Taylor said that he tells his patients to "avoid things that we know have a high level of bisphenol A," such as hard plastic water bottles and canned goods. This will help to lower BPA levels "until we start to see it taken out of all the things that we are not even aware of that we are exposed to every day."

Dr. Taylor reported a study in which he and his colleagues found that offspring of pregnant mice that had been injected with 5 mg/kg of BPA per day for a week had epigenetic changes in the methylation pattern of a gene involved in the uterine development. This altered methylation pattern, which was not seen in the offspring of control mice, resulted in a permanent increase in estrogen sensitivity, said Dr. Taylor, professor of obstetrics, gynecology, and reproductive sciences at Yale University, New Haven, Conn.

Other research, presented by Scott Belcher, Ph.D., of the University of Cincinnati, showed that BPA at nanomolar doses can act alone or in combination with estrogen to increase arrhythmic pulsing of ventricular cardiomyocytes from female rats and mice, as well as to increase the frequency of arrhythmias in whole hearts of female rats and mice.

A well-known researcher of BPA toxicology, Frederick vom Saal, Ph.D., of the University of Missouri, Columbia, also reported a study at the press briefing. He and his colleagues found that an orally administered dose of 400 mg/kg BPA is continually excreted and does not accumulate in the body of female rhesus macaques, a good model for human metabolism of chemicals such as BPA.

But the researchers found that the levels of biologically active BPA over a 24-hour period never dropped below average levels of the chemical that are found in people in the United States and other developed countries, suggesting that people are exposed to even higher levels. For people to have such high levels, they must be exposed to BPA from many unknown sources, Dr. vom Saal said, noting that 8-9 billion pounds of BPA are used in products worldwide each year.

Dr. Taylor argued that "we're not going to find unexposed human populations" to compare with exposed groups. "The human experiment will never be done [and] we can't afford to wait until we have perfect data in humans.

"When we see associations in humans mimicking exactly what we've proven are cause and effect in animals, I think that's pretty compelling," he added.

The National Institutes of Health funded the BPA studies and the scientific statement. Additional funding for the statement came from the European Commission, the Belgian Study Group for Pediatric Endocrinology, and grants from the Belgian Fonds de la Recherche Scientific Médicale. One author reported that he has served on the EPA advisory board, has received honoraria for university lectures, and has served as an expert witness in federal court. ■

A related video is at www.youtube.com/InternalMedicineNews (search for 67360).

Excess Weight Tied to 46% of Gestational Diabetes Cases

BY MIRIAM E. TUCKER

NEW ORLEANS — The proportion of gestational diabetes cases attributable to overweight and obesity totaled 46% in a population-based study of more than 20,000 women from seven U.S. states.

The data, from the Centers for Disease Control and Prevention's Pregnancy Risk Assessment Monitoring System (PRAMS), were used to generate a population-based estimate of the contribution of prepregnancy overweight and obesity to the development of gestational diabetes mellitus (GDM). Shin Y. Kim reported the results at the annual scientific sessions of the American Diabetes Association.

"If we assume that the relationship between GDM and obesity and overweight is causal and no other confounders exist, then a large proportion of GDM cases are potentially preventable," said Dr. Kim of the CDC's division of reproductive health.

She and her associates analyzed PRAMS data from the seven states that had implemented the 2003 revised birth certificate, which distinguishes GDM from diabetes that existed prior to pregnancy. The surveillance system collects data via a questionnaire from mothers of newborns 2-6 months after delivery. A total of 22,767 women with complete chart information who did not have pre-existing diabetes were included.

The overall GDM prevalence was 4%, ranging from 3.1% in Florida to 5% in Ohio. (The other five states were Nebraska, South Carolina, Utah, Washington, and New York, excluding New York City.) More than 70% of the women with GDM had a prepregnancy body mass index of at least 25 kg/m^2, compared with 44.9% of the women who did not have GDM during pregnancy, Ms. Kim reported.

The GDM prevalence was 0.7% for women classified as underweight (body mass index 13-18.4 kg/m^2) prior to pregnancy, 2.3% for those with normal weight (BMI 18.5-24.9), 4.8% for overweight women (25-29.9), 5.5% for those who were obese (30-34.9), and 11.5% for extremely obese women (35-64.9). With normal weight used as the reference group, the unadjusted relative risks of developing GDM were 2.1, 2.4, and 5 for women who were overweight, obese, and extremely obese, respectively.

"The probability of GDM increases with increasing BMI, with no clear BMI threshold below which a dose-response relationship was not evident," Ms. Kim said.

The relative risks did not change after adjustment for maternal age, race/ethnicity, marital status, or parity. Once adjusted, the proportions of gestational diabetes cases attributable to overweight, obesity, and extreme obesity were 15.4%, 9.7%, and 21.1%, for a total of 46.2%. "In other words, if all women with a BMI of 25 or greater had a GDM risk equal to that of women in the normal BMI category, nearly half of GDM cases could be prevented. Lifestyle interventions to reduce BMI have the potential to lower GDM risk," she commented.

There are a few possible reasons for why overweight/obesity contributed to only about half of GDM cases, Ms. Kim said in a follow-up interview.

"First, prepregnancy weight was self-reported, and women tend to underreport their weight. This may have led us to underestimate the contribution of overweight and obesity to the fraction of GDM attributable to weight. Also, there may be a race/ethnic difference in the relationship between BMI and GDM risk, and our analysis overrepresents non-Hispanic white women compared to the general population," she noted.

If the analyses had been done using data representing the entire U.S. population, she continued, the study might have generated a larger estimate of the proportion of GDM cases associated with a high BMI. "Physical activity also contributes to GDM risk, and we had no data on physical activity levels in our study population. In addition, BMI is not a perfect measure of body fat, but we use it often because it can easily be obtained. If we had used lean women as our reference group, the [attributable proportion] would have been much higher. This is because the GDM risk increased in a nearly linear fashion as BMI increased."

However, she said, the 46% estimate from this study is "higher than other non–population-based estimates found in the literature, and the dose-response relationship is consistent with estimates found in the general population with type 2 diabetes."

Ms. Kim stated that she had no disclosures to make. ■