Endocrine Disruptors: A Top Research Priority

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 this summer.

"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. And the reason for that is we believe that science has taken us up to a point where we are concerned," Dr. Robert M. Carey, president of the Endocrine Society, said at a press conference at the society's annual meeting.

Researchers at the meeting also presented new animal studies on the possible effects of bisphenol A (BPA) on cardiac arrhythmias and epigenetic imprinting during gestational development, as well as the possible continual exposure of the majority 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 the evidence of 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

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Bisphenol A, found in products such as plastic water bottles, was among the endocrine disruptors discussed at the meeting.

EDCs, so this is extremely important," said Dr. Carey, who noted 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.

The scientific statement is published in the June issue of Endocrine Reviews (2009;30: 293-342).

"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, which is a synthetic monomer 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.

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 development of the uterus. 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 conference. 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."

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 Medicale. 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. ■

Bariatric Surgery in Mother Yields Healthier Offspring

BY BRUCE JANCIN

GRAPEVINE, TEX. — Obese women who have bariatric surgery prior to pregnancy have less complicated gestations, and their children are markedly less obese than are siblings born prior to mom's surgery, according to a Canadian study.

"Less obesity is not even the most important finding—it's the improvement in their metabolic condition. Children born after their mother's surgery had 30% less insulin resistance compared to their brothers and sisters born before the surgery. Regarding other elements of the metabolic syndrome, they also had a 20% decrease in triglyceride levels, their HDL was increased by 12%, and their waist circumference to height ratio was 11% better," Dr. Picard Marceau reported at the annual meeting of the American Society for Metabolic and Bariatric Surgery.

The implication of these findings is that the propensity to develop obesity and the metabolic syndrome is transmitted through the generations not only via genetic factors, but also epigenetically through the intrauterine environment, said Dr. Marceau of Laval University, Quebec City. "Morbid obesity is a congenital and treatable disease. To curb the vicious cycle of the obesity epidemic, the focus must be put on pregnancy," he continued. "The emphasis should be shifted from preventing undernutrition in pregnancy to preventing overnutrition in our affluent society. Surgery before pregnancy is a good option."

He and his coworkers studied 37 very obese mothers who collectively gave birth to 56 children prior to undergoing a biliopancreatic diversion with duodenal switch (BPD) for weight loss and another 54 children afterward. To beef up the study size, the investigators added another 10 morbidly obese women who had all 23 of their children prior to the BPD and 10 others who had all 19 of their children post surgery. Children born before the mother's bariatric surgery have been prospectively followed on average to age 19 years, while those born post surgery have been followed to age 10.

The mothers' preoperative body mass index averaged 48.5 kg/m^2. Fifteen years after surgery, it was 31.4 kg/m^2. Moreover, their blood glucose levels at follow-up were 20% lower than presurgically, their triglycerides and LDL levels were down by more than 50% each, and HDL was up by 40%. Bariatric surgery had a dramatic effect on the course of subsequent pregnancies. Pregnancies prior to surgery were marked by 12 cases of gestational diabetes, 9 of preeclampsia, and 15 of hypertension requiring antihypertensive therapy; pregnancies after surgery had none. Gestational weight gain averaged 13.8 kg/m^2 in the presurgical period and 6.8 kg/m^2 in the postsurgical era.

The birth weight of the children born after mom's surgery was 17% lower than that of their siblings born prior to surgery. The incidence of macrosomia was reduced by 86%.

Strikingly, the prevalence of severe obesity as defined by a BMI above the 90th percentile for age and sex was 75% less in the children born after the mother's surgery than in those born before. Abdominal fat accumulated in the postsurgical children at a rate five times slower than in the siblings born prior to surgery.

The impact of the salutary postsurgical intrauterine environment differed in boys and girls. In boys, it was manifest mainly as less weight gain; boys born after the mother's surgery had an 86% lower prevalence of obesity than did their older brothers. In contrast, the main effects noted in girls born after the mother's surgery were a 40% reduction in insulin resistance and a 35% decrease in percent body fat compared with their sisters born presurgically. The study was supported by the Canadian Institute of Health Research. ■