Special Lecture

Effects of Preimplantation and Prenatal Exposure of Endocrine Disrupters on Next Generation

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As shown in "Our Stolen Future," endocrine disrupters affect reproductive function of wild animals. There are growing concerns on reduced reproductive functions in humans evidenced by decreasing sperm volume, increasing number of patients with infertility or endometriosis, abnormality of sex differentiation, and recent changes in sex ratio resulting in attention to the association between these human health effects and endocrine disrupters. This report presents the actual conditions of contamination with a endocrine disrupter, bisphenol A (BPA) widely used for the production of plastic products and the approaches to evaluate these from the viewpoint of a the effect on next generation. There is broad human exposure to BPA which is produced at over 2 billion pounds/year and can act at very low doses detected in the environment. We measured contamination of BPA in various kinds of human biological fluids by a novel enzyme-linked immunosorbent assay. Blood samples were obtained from healthy premenopausal women, women with early and full-term pregnancy, and umbilical cord at full-term delivery. Ovarian follicular fluids obtained during IVF procedures and amniotic fluids obtained at mid-term and full-term pregnancy were also subject to BPA measurements. BPA was present in serum and follicular fluid at approximately 1-2 ng/ml, as well as in fetal serum and full-term amniotic fluid, confirming passage through the placenta. Surprisingly, an approximately 5-fold higher concentration, 8.3 +/- 8.7 ng/ml, was revealed in amniotic fluid at 15-18 weeks gestation, compared with other fluids. These results suggest accumulation of BPA in early fetuses and significant exposure during the prenatal period, which must be considered in evaluating the potential for human exposure to endocrine-disrupting chemicals. Exposure of mouse fetuses to BPA at a dose typical for environmental exposure in humans recently was found to produce postnatal estrogenic effects: increased prostate gland weight and reduced daily sperm production in males, and accelerated growth and puberty in females. Thus we have employed a preimplantation mouse development model to study the possible effects of low doses of BPA. BPA both have positive and negative effects on embryo development in mice. Stimulatory effects of BPA were observed in the blastocyst formation rate at concentrations of 1 nM and 3 nM. The present study demonstrated that low concentrations of BPA, not dose dependent manner, exert stimulatory or inhibitory effects on preimplantation embryo development. These alterations in low doses may be mediated by ER α and ER β, present in mouse preimplantation embryos. When the blastocysts with or without BPA exposure were transferred to uterine horns of pseudopregnant recipient mice with no BPA treatment, the number of pups in a litter and body weight at birth did not differ significantly. At weaning on postnatal day 21, however, siblings treated with 1 nM BPA during preimplantation period (13.5 ± 1.6g) were significantly heavier than controls(9.7 ± 2.8g). These findings suggest that BPA may not only effect early embryonic development even at low, environmentally relevant doses, but also exert some late effects on postnatal development. However, much remains to be learned about suspected relationship between prenatal BPA exposure and unexplained phenomena in humans over the past half century, such as an increase in genital abnormality in boys, earlier sexual maturation in girls, a decrease in sperm count in adult men, and an increase in breast cancer in adult women.