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Perinatal Bisphenol-A Exposure May Affect Fertility

Exposure to a ubiquitous environmental chemical during pregnancy may impair reproductive capacity of female offspring, according to a study published online in advance of print on December 2 in Environmental Health Perspectives. Fertility decreased over time in female mice that had been exposed during fetal and neonatal (perinatal) development to doses of bisphenol-A (BPA) that were lower than or equal to human environmental exposure levels.

"Mice exposed to BPA in the womb and during nursing subsequently had fewer successful pregnancies and delivered fewer pups over the course of the study," reported one of the study's co-senior authors, Ana M. Soto, MD, Professor of Anatomy and Cellular Biology at Tufts University School of Medicine (TUSM) and Member of the Cell, Molecular and Developmental Biology Program faculty at the Sackler School of Graduate Biomedical Sciences.

At the highest of three doses tested, only 60% of the BPA-exposed mice had four or more deliveries over a 32-week period, compared with 95% in the unexposed control group. Decline of the reproductive capacity of the female mice in this study was not obvious at first pregnancy, when the animals were very young, but manifested later in life with a decline in number of pups born per delivery.

"This finding is important because standard tests of reproductive toxicology currently consist of assessing the success of a first pregnancy in young animals. If subsequent pregnancies are not examined, relevant effects may be missed," said co-senior author Beverly S. Rubin, PhD, Associate Professor of Anatomy and Cellular Biology at TUSM and member of the cell, molecular and developmental biology and neuroscience program faculties at the Sackler School.

"In addition, the infertility effect of BPA was dose-specific in our study. The lowest and highest doses we tested both impaired fertility, while the intermediate dose did not. This phenomenon, called non-monotonicity, is a common characteristic of hormone action. In other words, chemicals have to be tested at a variety of doses in order to avoid false "no effect" results," added co-senior author Carlos Sonnenschein, MD, Professor of Anatomy and Cellular Biology at TUSM and Member of The Cell, Molecular and Developmental Biology Program faculty at the Sackler School.

"BPA has effects that mimic those of estrogen, a natural hormone. Fetal and neonatal exposure to BPA has been shown to have other hormone-related effects in rodents, including increased risk of mammary and prostate cancers, altered behavior, and obesity. BPA has been found in the urine of over 92% of Americans tested, with higher levels in children and adolescents relative to adults. It has also been detected in human maternal and fetal plasma," said co-first author Perinaaz R. Wadia, PhD, a Research Associate in the Soto/Sonnenschein laboratory at TUSM.

"Our findings are potentially of great relevance to humans because BPA is used in the production of materials people are exposed to every day, such as polycarbonate plastics and the resins used to coat the inside of food and beverage cans," said co-first author Nicolas J. Cabaton, PhD, formerly a Post-doctoral Fellow in the Soto/Sonnenschein laboratory at TUSM and now at the French National Institute for Agricultural Research (INRA).

The authors compared the effects of BPA to those of diethylstilbestrol (DES), a hormonally active chemical that is known to have caused reproductive impairment in women exposed during fetal life, and concluded that the effects of these two chemicals on fertility were comparable. Similar to BPA, low doses of DES had failed to cause obvious reproductive problems, when evaluated only at first pregnancy as in the standard tests used by regulatory agencies to determine toxicity.

The three doses of BPA tested are within the range of human exposure and below the Environmental Protection Agency reference dose (i.e., the maximal acceptable daily dose). "Our results suggest that a more sensitive test, like the one used in this report should be adopted by regulatory agencies in order to uncover the true risk and possible epigenetic effects of suspected endocrine disruptors," said Soto.

Additional authors include Daniel Zalko, DVM, PhD, French National Institute for Agricultural Research Cheryl M. Schaeberle, BS, Laboratory Coordinator in the Soto/Sonnenschein lab; Michael H. Askenase, BS, formerly a Research Technician in the Soto/Sonnenschein lab; Jennifer L. Gadbois, RN, Andrew P. Tharp, BS, and Gregory S. Whitt, BS, all research technicians in the Soto/Sonnenschein lab in the department of anatomy and cellular biology at TUSM.

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