Surrogate Markers of in utero Exposure to Xenobiotics

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There is growing concern that in utero exposures to environmental chemicals are causal factors behind increasing trends in adverse health outcomes, such as developmental abnormalities of the male reproductive tract. We proposed, however, that traditional approaches to exposure assessment are biased towards the quantification of relatively inactive chemical contaminants, as opposed to dietary and lifestyle factors that may be more relevant to the pathogenesis of adverse developmental outcomes. We hypothesized that fetal exposure to background levels of environmental contaminants is too low to be causally associated with adverse health outcomes in the human population. We tested this hypothesis by conducting the following activities central to elucidating the role of environmental agents in fetal development:

1. Pregnant women attending the McMaster University Medical Centre during their first trimester ultrasound assessment were recruited for this study, which was designed to quantify exposure to environmental contaminants. Maternal blood and urine, umbilical cord blood, and placental samples were obtained from women who agreed to participate in this study. All of the enrolled women provided informed consent, and study procedures were approved by the McMaster University research ethics board. The samples collected were used to determine the most relevant tissue compartment to sample for the assessment of in utero exposure to environmental chemicals. No study subjects were intentionally exposed to any of the target analytes in this study and routine questionnaires were employed to try and identify sources and routes of exposure.

2. Cell based assay systems were utilized to biologically characterize patient serum samples, which directed subsequent analytical approaches to quantify in utero exposure to chemicals (man-made and naturally occurring) acting through key mechanistic pathways.

3. Maternal serum was analyzed for a battery of potential biomarkers of fetal and placental development. In addition, gene microarrays and Real-Time Polymerase Chain Reaction examined placental tissue obtained at birth for expression patterns of novel gene biomarkers of exposure.

Our results demonstrated that human developmental exposure to perfluoroalkanes (PFCs) and polybrominated diphenylethers (PBDEs) is low, providing government agencies with data essential for making risk-based decisions. Residue levels were not associated with any obstetrical complications or adverse effects on fetal development. However, morphological changes in the placenta were found in women who smoked 10 or more cigarettes during pregnancy. Glucose transporter protein-1 levels were lower in women who smoked compared to non-smokers, suggesting impaired glucose transport which may explain lower birth weight in offspring of women who smoke during pregnancy. These findings have led to an animal study which revealed that developmental exposure to nicotine attenuates connexin-26 expression and thus may play a role in diminished glucose transport across placental membranes.

Implications: Human exposure to emerging contaminants (e.g., PFCs and PBDEs) and lifestyle factors, such as cigarette smoke constituents, were documented in the serum and urine of pregnant women and in umbilical cord blood. Successful completion of this project within a three-year period provided context regarding human in utero exposure to environmental agents for policy makers, regulators, health care providers, and patients so that informed, risk-based decisions can be made.

Key words: in utero exposure, perfluoroalkanes, polybrominated diphenylethers, serum

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Foster, W.G., Holloway, A.C., and Hughes Jr., C.L. (2005). Dioxin-like activity and maternal thyroid hormone levels in second trimester maternal serum. *American Journal of Obstetrics and Gynecology* 193: 1900-1907. (This article was featured by the editor together with a commentary by a clinical colleague).


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