

Surrogate Markers of *in utero* Exposure to Xenobiotics

Warren G. Foster. *McMaster University, University of Ottawa, University of Calgary.*

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 propose, 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 hypothesize 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 addressing three questions central to elucidating the role of environmental agents in fetal development. First, pregnant women attending the McMaster University Medical Centre their first trimester ultrasound assessment were recruited for this study. In women who agreed to participate in this study, maternal blood and urine, umbilical cord blood and placental samples were obtained from women enrolled in a study designed to quantify exposure to environmental contaminants. All women provided informed consent and 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. Second, we utilized cell based assay systems 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. Finally, 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. 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 decisions can be made.

Implications: Human exposure to emerging contaminants (Perfluoroalkanes (PFCs) and Polybrominated Diphenylethers (PBDEs)) and lifestyle factors were documented by examining cigarette smoke constituents in the serum and urine of pregnant women and in umbilical cord blood. Our results demonstrate that human developmental exposure to PFCs and PBDEs is low, providing government agencies with data essential for risk assessment. Residue levels were not associated with any 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.

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Presentation(s):

Foster, W.G. (2003). *In utero* exposure to endocrine toxicants and dietary phytoestrogens. Linus Pauling Institute, Oregon State University, Corvallis, OR, December 18, 2003.

Foster, W.G. (2005). Reproductive effects of environmental endocrine toxicants. First Sino-Canada Bilateral Workshop on Reproductive Health Research, Beijing, China, November 15-18, 2005.

Neal, M.S., Petrik, J., Foster, W.G., and Holloway, A.C. (2005). *In utero* and lactational exposure to nicotine: Ovarian effects. Conjoint American Society of Reproductive Medicine and Canadian Fertility & Andrology Society Meeting, Montreal, QU, October 16-19, 2005. Best Basic Science Paper and Alpha Award.

Neal, M.S., Zhu, J., and Foster, W.G. (2005). Quantification of benzo-[a]-pyrene (B[a]P) in serum and follicular fluid and its effects on follicle growth in an isolated follicle culture assay. Conjoint American Society of Reproductive Medicine and Canadian Fertility and Andrology Society Meeting, Montreal, QU, October 16-19, 2005.

Monroy, R., Bourgeois, J., Shaw, D., Morrison, K., Teo, K., Atkinson, S., and Foster, W.G. (2007). Effects of maternal smoking on the placenta vasculosyncytial membrane thickness. 13th International Federation of Placenta Associations, Kingston, Ontario, August 17-22, 2007. Poster of Mention and Y. W. Loke New Investigator Award.

Monroy, R., Bourgeois, J., Shaw, D., Morrison, K., Atkinson, S., Teo, K., and Foster, W.G. (2008). Effects of cigarette smoking in pregnancy on the placenta vasculosyncytial membrane thickness. 47th Annual Meeting of the Society of Toxicology, Seattle Washington, March 16-20, 2008.

***Peer-reviewed publication(s):**

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).

Foster, W.G. (2008). Fetal and early postnatal environmental contaminant exposures and reproductive health effects in the female. *Fertility and Sterility* 89(2 Suppl): e53-54.

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Neal, M.S., Zhu, J., and Foster, W.G. (2008). Quantification of benzo-[a]-pyrene in the serum and follicular fluid of smoker vs. non-smokers. *Reproductive Toxicology* 25: 100-106.

*Two articles are in preparation.

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