

Drinking Water Contaminants, Gene Polymorphisms, and Fetal Growth

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There are still many uncertainties regarding the risk of adverse pregnancy outcomes associated with exposure to drinking water disinfection by-products. In Montréal, Québec, Canada, we carried out a hospital-based case-control study including 493 cases of intrauterine growth restriction defined as birth weight below the 10th percentile for gestational age and sex, according to Canadian standards. Controls were babies ($n = 472$) delivered at the same hospital whose birth weight was at or above the 10th percentile, matched for gestational age, race, and sex. Exposure to total and specific trihalomethanes was measured using regulatory data collected by municipalities and the provincial Ministry of Environment. Residential history, water drinking, and shower habits during pregnancy, as well as known risk factors for intrauterine growth restriction, were measured with a face-to-face interview with all mothers. Mothers and newborns were characterized for two genetic polymorphisms, one in the *CYP2E1* gene (G1259C), and another in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene (C677T). Exposure to specific and total trihalomethanes from drinking water, determined for 458 cases and 426 controls, did not result in an increased risk of intrauterine growth restriction. However, significant effect modification was observed between newborns with and without the *CYP2E1* variant; among newborns with the variant, the adjusted odds ratio for intrauterine growth restriction associated with exposure to average total trihalomethanes above the 90th percentile (corresponding to 29.4 µg/L) was 13.20 (95% confidence interval, 1.19–146.72). These findings suggest that exposure to trihalomethanes at the highest levels can affect fetal growth but only in genetically susceptible newborns. **Key words:** *CYP2E1* gene, disinfection by-products, drinking water, gene polymorphism, gene-environment interaction, intrauterine growth restriction, low birth weight, *MTHFR* gene, trihalomethanes. *Environ Health Perspect* 112:1213–1216 (2004). doi:10.1289/ehp.7003 available via <http://dx.doi.org/> [Online 26 May 2004]

Chlorination by-products in drinking water come from the reaction of chlorine with organic material in the water. This reaction occurs naturally or originates from municipal, agricultural, and industrial wastes. Trihalomethanes (THMs) such as chloroform, bromoform, bromodichloromethane (BDCM), and chlorodibromomethane are the most prevalent class of disinfection by-products (DBPs) found in treated water. From the toxicologic literature, chloroform appears to affect fetal development (Geveker Graves et al. 2001), by mechanisms that have not yet been elucidated. In the last decade, a number of epidemiologic studies have been carried out to determine the effect of DBPs on adverse pregnancy outcomes (Bove et al. 2002). Two recent reviews propose that the weight of the evidence, although moderate and not fully conclusive, is in favor of an association between DBPs and fetal growth restriction (Bove et al. 2002; Geveker Graves et al. 2001). Most of the previous studies were based on information from birth records, and despite the fact that the number of records included was usually large, the information that was available on other risk factors for fetal growth, or on other personal variables influencing exposure to DBPs, was often limited.

The primary enzyme involved in the metabolism of low doses of chloroform is *CYP2E1* (Meek et al. 2002). My group has previously shown that a polymorphism in the

CYP2E1 gene can modify the effect of water contaminants (Infante-Rivard et al. 2002a). Another enzyme, 5,10-methylenetetrahydrofolate reductase (*MTHFR*), together with folic acid, is involved in the remethylation of homocysteine to methionine, as well as in the methylation of DNA, proteins, and phospholipids (Botto and Yang 2000). Alston (1991) reported that vitamin B₁₂-dependent methionine biosynthesis could be inhibited by chloroform. Common polymorphisms in the *MTHFR* gene have been identified (Botto and Yang 2000). To my knowledge, no study has considered the role of genetic polymorphisms on the relationship between DBPs and fetal growth.

My group carried out a study on genetic and metabolic risk factors for intrauterine growth restriction (IUGR) (Infante-Rivard et al. 2002b, 2003a, 2003b). In the course of the study, we also collected personal and environmental information to analyze the association between chemical water contaminants and fetal growth.

Materials and Methods

Study subjects. Details on study subjects have been reported elsewhere (Infante-Rivard et al. 2002b). Briefly, cases were newborns whose birth weight was below the 10th percentile for gestational age and sex, based on Canadian standards (Arbuckle et al. 1993). All cases seen at the largest university-based mother-child

center in Montréal between May 1998 and June 2000 who were born singleton, alive after the 24th week of gestation, and without severe congenital anomalies were eligible for the study. During that period, 505 newborns met the eligibility criteria, and 493 were included in the study (97.6%). Controls were born at the same hospital and met the same eligibility criteria, except that their birth weight was at or above the 10th percentile. They were matched to cases for gestational week, sex, and race (white, black, Hispanic/Amerindian, and Asian) and usually born within 1 week of the matched case subject. Of those identified, 480 controls were invited to participate, and 472 accepted (98.3%). The project was approved by the hospital ethics committee. An informed consent was signed by the mother to collect cord and maternal blood.

Interview. A face-to-face interview with all mothers of cases and controls was carried out in French or English at the hospital, generally within 2 days of delivery. It included questions about demographic factors, complications of pregnancy, maternal chronic diseases, obstetric history, and smoking. The medical record was used for variables such as height and weight and to confirm pregnancy diseases. To determine exposure to water contaminants for each pregnancy trimester until delivery, we collected the following information: maternal residential history, source of drinking water (community, private well, bottled), use and type of domestic water filter, average number of glasses of water per day at home or elsewhere (including those with reconstituted frozen fruit juices), usual way of consuming tap water (directly from tap, after refrigeration), average number of showers per week, and usual duration of showers.

Exposure ascertainment. For the study period, exposure to THMs from drinking water according to place of residence was obtained from regulatory data collected by municipalities and the Ministry of Environment. There were 189 distribution systems involved;

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