Environment International 120 (2018) 231–237

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Impact of exposure to phenols during early pregnancy on birth weight in two Canadian cohort studies subject to measurement errors☆

Fiona Lester[a], Tye E. Arbuckle[b], Yingwei Peng[c,a,*], Michael A. McIsaac[d]

[a] Department of Mathematics and Statistics, Queen's University, Kingston, Ontario, Canada
[b] Health Canada, Population Studies Division, Environmental Health Science and Research Bureau, Health Canada, 101 Tunney's Pasture Drive, Tunney's Pasture, Ottawa, Ontario, Canada
[c] Department of Public Health Sciences, Queen's University, Kingston, Ontario, Canada
[d] School of Mathematical and Computational Sciences, University of Prince Edward Island, Charlottetown, PEI, Canada

ARTICLE INFO

Handling Editor: Lesa Aylward

Keywords:
Measurement error
Regression calibration
Intra-class correlation coefficient
Gestational age
Bisphenol A
Triclosan

ABSTRACT

Background: It is of interest to know whether early pregnancy exposure to phenols such as bisphenol-A (BPA) or triclosan (TCS) negatively impacts birth weight outcomes. Exposure to these chemicals is widespread in the Canadian population but obtaining accurate measurements of average exposure is difficult because these chemicals are rapidly excreted from the body, causing body levels to fluctuate both within and between days, as observed in a recent Canadian study (P4). This measurement error can attenuate the estimated effects of exposures.

Methods: Data from two Canadian cohort studies, the Plastics and Personal-care Products use in Pregnancy (P4) Study and the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, such that all participants with complete BPA or TCS exposure and outcome data were used (MIREC $n = 1822$, P4 $n = 68$). We used regression calibration to correct for the attenuating effects of exposure measurement error when modeling the effect of first trimester BPA or TCS exposure on four birth weight outcomes: birth weight (BW), low birth weight (LBW), small for gestational age (SGA) and large for gestational age (LGA). Specific gravity, time of day, and time since last urine void were also controlled in the analysis.

Results: TCS exposure has a marginally significant association with SGA only with odds ratio 0.87 and 95% confidence interval (0.74, 1.00). It also has a marginally significant association with LGA in male offspring with odds ratio 1.11 and 95% confidence interval (1.00, 1.25). The effects of BPA on the four birth outcomes were insignificant.

Conclusions: Increased TCS exposure during pregnancy is marginally associated with decreased odds of having SGA offspring. It is possibly associated with decreased BW in males and decreased odds of LBW, though these associations were not present in measurement error corrected models. TCS is possibly associated with increased odds in male offspring of being LGA, though this relationship was not present in models not corrected for measurement error. The study finds no significant effects of BPA on birth weight outcomes, which may be due to more severe measurement error in a single observation of BPA.

1. Introduction

Low birth weight (LBW) and small for gestational age (SGA) are well-known risk factors for perinatal illness and death, and are associated with long-term morbidity (Kidder et al., 2000). There are many known risk factors for LBW (e.g. young maternal age, low education level) and SGA (e.g. maternal smoking during pregnancy, gestational hypertension), but it is of interest to increase understanding of additional potential risk factors for adverse birth weight outcomes (McCowan and Horgan, 2009; Shmueli and Cullen, 1999). Exposure to various environmental chemicals such as triclosan (TCS) and bisphenol-A (BPA) during early pregnancy is a proposed risk factor.

Exposure to the chemical BPA is common in the Canadian population. Detectable concentrations of BPA were present in the urine of 92% of Canadians in the most recent Canadian Health Measures Survey (Health Canada, 2015). Exposure occurs through materials such as

☆ Competing Financial Interests: The authors declare that they have no competing interests.

* Corresponding author at: Department of Public Health Sciences, Queen's University, Kingston, ON K7L 3N6, Canada.
E-mail address: pengp@queensu.ca (Y. Peng).

https://doi.org/10.1016/j.envint.2018.08.005
Received 17 February 2018; Received in revised form 2 August 2018; Accepted 2 August 2018

polycarbonate plastic, epoxy resins that coat cans, and dental fillings (Arbuckle et al., 2014). Research into the potential endocrine disrupting effects of BPA has been extensive over the past decade but studies display conflicting results specific to the effect of maternal exposure on pregnancy outcomes (Birks et al., 2016; Casas et al., 2016; Chou et al., 2011; Ferguson et al., 2016; Huo et al., 2015; Philippat et al., 2012, 2014; Tang et al., 2013; Troisi et al., 2014; Snijder et al., 2013; Wolff et al., 2008).

Triclosan (TCS) is also a common chemical, with about 65% of the Canadian population exposed to detectable concentrations in urine (Health Canada, 2015). TCS is anti-microbial and is therefore found in products such as soap, toothpaste, mouthwash, deodorant, lotion, and acne face washes. It is also used as a preservative in materials such as textiles, rubber, and plastic (Government of Canada, 2013). TCS has been less investigated in the literature, with fewer existing studies investigating associations between maternal exposures and pregnancy outcomes and only one to our knowledge reporting any significant association between TCS exposure and birth weight or gestational age (Etzel et al., 2017; Geer et al., 2017; Lassen et al., 2016; Philippat et al., 2012, 2014; Wolff et al., 2008). Etzel et al. (2017) averaged urinary TCS exposure over two samples at 16 weeks and 26 weeks for 378 pregnant women and found that increased TCS was associated with decreased birth weight. The remainder of the studies utilized a single urine sample to quantify TCS exposure and found no association with birth weight.

Both BPA and TCS are excreted primarily through urine and do not accumulate in the body (Sandborgh-Englund et al., 2006; Völkel et al., 2002). BPA has a reported half-life of 5.3 h, whereas TCS has a slightly longer half-life of around 11 h (Genuis et al., 2012; Sandborgh-Englund et al., 2006). Substances with short half-lives are rapidly eliminated from the body and therefore their levels in urine samples exhibit high variability when measured repeatedly in the same subject throughout the day. This leads to increased measurement error when single spot urine samples are used to capture average exposure levels (Lin et al., 2005). Additionally, BPA and TCS exposure occur episodically throughout the day, which further increases the measurement error that can occur when single spot urine samples are used.

As the ratio of between-individual variance to within-individual variance decreases, the ability to accurately reflect a long-term average exposure using a single measurement decreases (Lin et al., 2005). This is often quantified using an intra-class correlation coefficient (ICC), defined as the ratio of the variance between individuals to the sum of the variance between and within individuals (Pleil and Sobus, 2013). ICCs, which fall between 0 and 1 with higher values representing more reliable exposure measurements, therefore, tend to be higher for substances with longer half-lives. Past studies analyzing repeated spot-urine samples show that TCS and BPA exhibit very different ICCs. For BPA, reported ICCs typically range from 0.1 (e.g. 389 pregnant women sampled at 16 weeks, 26 weeks, and delivery (Braun et al., 2011)) to 0.5 (e.g. 25 children, 4 samples over 2 days (Heffernan et al., 2014)), with a greater proportion falling closer to 0.1 (Fisher et al., 2015). Fewer studies have investigated TCS ICCs. Lassen et al. (2013) measured 4 samples over 3 months in men and found ICCs between 0.55 and 0.9. Koch et al. (2014) measured every void over 6 days and calculated an ICC of 0.934. Philippat et al. (2014) measured 3 samples at least 2 weeks apart in 71 women and obtain ICCs of 0.56, 0.58, and 0.60 respectively, depending on whether the ICC was unadjusted, adjusted for specific gravity alone, or adjusted for specific gravity (a measure that attempts to control for differences in the hydration status of the participants at the time of sampling) and hour of sampling.

Therefore, measurement error is an important concern when using a measurement from a single spot urine sample as a proxy for average exposure to BPA or, to a lesser extent, TCS. Recent studies suggested that some of the variability in TCS and BPA exposure is due to differences in time of day of the sample and how recently the participant last urinated. Specifically, samples collected after 16:00 showed higher levels of both TCS and BPA, and samples collected when the time since the participant's last urine void was greater than 90 min showed higher levels of TCS (Fisher et al., 2015; Weiss et al., 2015). Therefore these variables, along with specific gravity, could explain some of the variation in exposure levels within participants.

In this paper we explore the variability of repeated BPA and TCS measurements within individuals over the course of one or two days during early pregnancy (< 20 weeks gestation) using the Plastics and Personal-care Products use in Pregnancy (P4) Study, a recent Canadian study (Arbuckle et al., 2015b). We also look for association between TCS or BPA exposure in early pregnancy and four birth weight outcomes (birth weight (BW), LBW, SGA, and large for gestational age (LGA)) using combined data from both the P4 Study and the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, another recent Canadian study (Arbuckle et al., 2013). We use the regression calibration technique to correct for the attenuating effects of the measurement error in BPA and TCS when modeling their effects on birth weight outcomes.

2. Methods

The MIREC Study was designed as a Canadian biomonitoring study for pregnant women and their babies to investigate possible adverse health effects of exposure to a wide range of environmental chemicals during pregnancy. One of the specific objectives of the MIREC Study was to assess if exposure to either BPA or TCS during early pregnancy has negative impacts on birth outcomes. MIREC recruited participants from 2008 to 2011 and obtained a single spot urine sample from a cohort of 2000 pregnant women (Arbuckle et al., 2013). Since the explanatory variable of interest in our study was mean exposure over all of early pregnancy, there was likely considerable measurement error in using this single observation as a proxy. The P4 Study was designed to evaluate the variability in BPA and TCS measurements. P4 recruited participants from 2009 to 2010 and collected multiple urine samples from each of the 80 pregnant women during the early pregnancy (< 20 weeks) as well as information about the pregnancy outcome. It is possible that other exposure measures may alternatively be the relevant exposure, such as median or maximum early pregnancy exposure, but these were not explored here. Informed consent was obtained from all subjects of the MIREC and P4 studies.

We focused on four outcomes: BW, LBW, SGA, and LGA. LBW was defined as a birth weight less than 2500 g (World Health Organization, 1992) for both male and female babies. LBW encompassed both babies who were small because they were born preterm and those who were small because of restricted intrauterine growth. In order to specifically investigate LBW caused by restricted intrauterine growth, gestational age (GA) must be controlled for. Babies with low BW, controlling for gestational age, are referred to as SGA (Kidder et al., 2000). Conversely, babies with high BW for their gestational age are called LGA. The sex-specific 10th and 90th percentile values from the fetal growth references of Kramer et al. (2001) were used as our cut-off values for defining SGA and LGA, respectively, and these dichotomous outcomes were analyzed separately from each other.

A spot urine sample to measure TCS and BPA was taken 6–13 weeks after conception in the MIREC study, while in the P4 study, all urine voids during a 24-h period before 20 weeks of pregnancy were collected. Some participants in the P4 study chose to participate in two separate 24-h collection days. Urine samples were measured for TCS and BPA concentration using a gas chromatographic tandem mass spectrometric method. At delivery, BW was recorded. GA at delivery was calculated using both first trimester ultrasound and last menstrual period. If the GA calculated by first trimester ultrasound differed by more than 7 days from the GA calculated by the last menstrual period, then the ultrasound GA was used and otherwise the last menstrual period GA was used. Ultrasound GA was calculated by adding gestational age in days as recorded at first ultrasound to the number of days between the first ultrasound and delivery. Other confounders, such as