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Associations between maternal triclosan concentrations in early pregnancy and gestational diabetes mellitus, impaired glucose tolerance, gestational weight gain and fetal markers of metabolic function

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ABSTRACT

Background: Triclosan is a phenolic biocide used in a multitude of consumer products and in health care settings. It is widely detected in the American and Canadian populations and has been shown in animal models to act as an endocrine disrupting agent. However, there has been little examination to date of the effects of triclosan exposure in pregnancy on perinatal metabolic outcomes in human populations.

Methods: Using data from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a Canadian pregnancy cohort, we measured associations of first-trimester urinary triclosan concentrations with total gestational weight gain, gestational diabetes mellitus and impaired glucose tolerance in pregnancy, and fetal markers of metabolic function. Leptin and adiponectin were measured in plasma from umbilical cord blood samples in term neonates and categorized into low (< 10th percentile), intermediate (10th–90th percentile) and high (> 90th percentile) levels. Triclosan concentrations were grouped into quartiles and associations with study outcomes were examined using logistic regression models with adjustment for maternal age, race/ethnicity, pre-pregnancy BMI, education and urinary specific gravity. Restricted cubic spline analysis was performed to help assess linearity and shape of any dose-response relationships. All analyses for leptin and adiponectin levels were performed on the entire cohort as well as stratified by fetal sex.

Results: Triclosan measures were available for 1795 MIREC participants with a live born singleton birth. Regression analyses showed a non-significant inverse association between triclosan concentrations and leptin levels above the 90th percentile that was restricted to female fetuses (OR for highest quartile of triclosan compared to lowest quartile = 0.4 (95% CI 0.2–1.1), p-value for trend across quartiles = 0.02). Triclosan concentrations in the second quartile were associated with elevated odds of adiponectin below the 10th percentile in male fetuses (OR for Q2 compared to Q1 = 2.5, 95% CI 1.1–5.9, p-value for trend across quartiles = 0.93). No significant linear associations between triclosan concentrations and leptin or adiponectin levels in overall or sex-specific analyses were observed from restricted cubic spline analyses. No significant associations were observed in adjusted analyses between triclosan concentrations and gestational diabetes mellitus, impaired glucose tolerance or gestational weight gain.

Abbreviations: CV, coefficient of variation; GCT, glucose challenge test; GDM, gestational diabetes mellitus; GWG, gestational weight gain; IGT, impaired glucose tolerance; IOM, Institute of Medicine; MCPP, mono-(3-carboxypropyl) phthalate; MIREC, Maternal-Infant Research on Environmental Chemicals; OGTT, oral glucose tolerance test; SG, specific gravity

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Conclusions: This study does not support an association between triclosan concentrations in pregnancy and fetal metabolic markers, glucose disorders of pregnancy, or excessive gestational weight gain.

1. Introduction

Triclosan is a broad-spectrum, phenolic biocide with activity against bacteria and fungi and is used in consumer products (Health Canada and Environment Canada, 2012) and health care settings (Jones et al., 2000; MacIsaac et al., 2014). Triclosan is widely detected in the American (Calafat et al., 2008) and Canadian (Health Canada, 2013) populations, with primary exposure through ingestion or dermal contact (Wittassek et al., 2011; Environment and Climate Change Canada and Health Canada, 2016). It has a similar structure to known endocrine disrupting chemicals (Dann and Hontela, 2011), and some studies in animals suggest it may act as an endocrine disrupting agent (Health Canada and Environment Canada, 2012; Wang and Tian, 2015) and may impact metabolism (Guo et al., 2012; Lankester et al., 2013). Triclosan may also affect thyroid function (Lankester et al., 2013), which in turn has been associated with gestational diabetes mellitus (GDM) and low birth weight (Karakosta et al., 2012). While triclosan has been associated with metabolic outcomes in non-pregnant adults (Lankester et al., 2013; Li et al., 2015), examination to date of its effects on perinatal outcomes has been limited and has been mostly related to neonatal size and growth parameters (Wolff et al., 2008; Philippat et al., 2012, 2014; Geer et al., 2016; Lassen et al., 2016), with little attention given to maternal and fetal metabolic outcomes (Buckley et al., 2016).

Evidence has shown sex-specific effects of triclosan in animal (Wang and Tian, 2015) and human (Wolff et al., 2008) studies. In addition, studies examining leptin and adiponectin have found differences by fetal sex (Kajantie et al., 2004; Mantzoros et al., 2009; Karakosta et al., 2013; Luo et al., 2013; Volberg et al., 2013). Accordingly, the objective of the present study was to assess associations between triclosan concentrations, as measured in first-trimester pregnancy urine samples, and perinatal metabolic outcomes including gestational weight gain (GWG), glucose disorders in pregnancy (GDM and impaired glucose tolerance (IGT) in pregnancy) and fetal markers of metabolic function (leptin and adiponectin, as measured in venous umbilical cord blood), and to examine these associations with stratification by infant sex.

2. Material and methods

2.1. Study sample

The Maternal-Infant Research on Environmental Chemicals (MIREC) Study is a longitudinal birth cohort study conducted across Canada. Further details concerning inclusion and exclusion criteria and study objectives and procedures have been published elsewhere (Arbuckle et al., 2013). Briefly, women were recruited before 14 weeks gestation from 10 Canadian cities between 2008 and 2011. The present analyses were limited to participants who had not withdrawn from the study (18 women excluded) and who had a live singleton birth (49 live multiple births, 32 spontaneous abortions, 13 therapeutic abortions and 9 stillbirths excluded). During the first visit (< 14 weeks gestation), participants provided a urine and blood sample and completed a questionnaire requesting information on demographic and lifestyle factors. For associations with GDM and IGT, participants with pre-existing diabetes (n = 24) and women who did not have a glucose challenge test (GCT) or an oral glucose tolerance test (OGTT) to determine a diagnosis of GDM and IGT (n = 586) were excluded. Leptin and adiponectin analyses were conducted only for women who had a cord blood sample collected after delivery (708 women without cord blood samples excluded). Preterm infants (n = 54) were excluded from these analyses, as leptin and adiponectin levels were notably lower prior to 37 weeks gestation, as has been reported previously (Kajantie et al., 2004).

2.2. Triclosan measurement

For triclosan analyses, sensitive LC-MS/MS methods were developed for the analysis of free and conjugated forms of triclosan in urine. The intraday coefficients of variation (CV) ranged from 2.5% (free triclosan and triclosan sulfate) to 4.5% (triclosan glucuronide), and the interday CVs ranged from 4.3% (triclosan sulfate) to 13% (triclosan glucuronide) (Provencher et al., 2014). Detailed quality assurance/quality control procedures are described in Provencher et al. (Provencher et al., 2014). To account for urine dilution, the specific gravity was measured in thawed urine samples by a refractometer (UG-1, Atago 3461; Atago U.S.A.). Statistical analyses were conducted based on total triclosan concentrations, obtained by summing free triclosan, triclosan glucuronide, and triclosan sulfate. Machine readings were used for 12 samples below the limit of detection (0.12 μg/L), as has been done in previous studies (Zhang et al., 2015; Holland et al., 2016). Further details on triclosan analyses in the MIREC cohort have been previously published (Arbuckle et al., 2015).

2.3. Study outcomes

Total GWG was categorized as defined by the U.S. Institute of Medicine (IOM) (Institute of Medicine US and National Research Council US Committee to Reexamine IOM Pregnancy Weight Guidelines, 2009). For approximately 10% of MIREC study participants, the last measured weight prior to delivery was four or more weeks prior to the delivery date and, therefore, not a reliable proxy for delivery weight. Accordingly, we calculated GWG based on the rate of weekly gain during the second and third trimesters, as this method does not rely on the last measured weight prior to delivery being an accurate representation of delivery weight. The rate of weekly weight gain was calculated by dividing the weight gain between the first trimester visit and the last measured weight before delivery by the number of weeks intervening between these two measures (Ashley-Martin et al., 2016). Further details on the calculation of GWG are described in Dzakpasu et al. (2015).

IGT and GDM were assessed by chart review based on the results of a 50 g GCT and a 75 or 100 g OGTT, in accordance with guidelines from the Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada (Berger et al., 2002; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008) and as described in our previous work with this cohort (Shapiro et al., 2015). Briefly, if the result of the 1-h 50 g GCT was ≥ 10.3 mmol/L or if at least two of the cut-off values were met or exceeded on a 75 g or 100 g OGTT, a diagnosis of GDM was assigned. Gestational IGT was diagnosed if one of the OGTT cut-off values was met or exceeded.

Leptin and adiponectin were measured in plasma from umbilical cord blood samples. Analysis was done by ELISA at Mt. Sinai Laboratory (Toronto, ON, Canada) using assay kits from Meso Scale Discovery (MSD) (Rockville, MD, USA). All samples with coefficient of variation (CV) greater than 15% were repeated. The inter- and intra-assay CVs were 11.8% and 9.3% respectively for leptin and 8% and 9% respectively for adiponectin. All samples were in the range of detection.

Umbilical cord blood levels of leptin and adiponectin were categorized into < 10th percentile, 10th–90th percentile, and > 90th percentile. Due to differing leptin levels among male and female neonates,