Environment International 120 (2018) 54–62

Contents lists available at ScienceDirect

Environment International

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

The association of repeated measurements of prenatal exposure to triclosan with fetal and early-childhood growth

Chuansha Wu[a,1], Jiufeng Li[b,1], Wei Xia[a], Yuanyuan Li[a], Bin Zhang[c], Aifen Zhou[c], Jie Hu[a], Chunhui Li[a], Hongzhi Zhao[b], Minmin Jiang[a], Chen Hu[a], Jiaqiang Liao[a], Wenqian Huo[d], Xi Chen[a], Bing Xu[a], Shi Lu[e], Zongwei Cai[b,**], Shunqing Xu[a,*]

[a] Key Laboratory of Environment and Health, Ministry of Education, Ministry of Environmental Protection, State Key Laboratory of Environmental Health, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China
[b] State Key Laboratory of Environmental and Biological Analysis, Department of Chemistry, Hong Kong Baptist University, Hong Kong, SAR, People's Republic of China
[c] Women and Children Medical and Healthcare Center of Wuhan, Wuhan, Hubei, People's Republic of China
[d] Department of Occupational and Environmental Health, College of Public Health, Zhengzhou University, Zhengzhou, Henan, People's Republic of China
[e] Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, People's Republic of China

ARTICLE INFO

Keywords:
Triclosan
Repeated measurements
Fetal growth
Early-childhood growth

ABSTRACT

Background: Triclosan (TCS) is known to possess endocrine disrupting properties and metabolize rapidly in the human body. Human data concerning repeated measurements of TCS throughout pregnancy in relation to fetal and childhood growth are sparse.

Objectives: We investigated the associations between multiple measurements of maternal urinary concentrations of TCS during pregnancy and fetal and early-childhood growth.

Methods: The study population included 850 mother-infant pairs who participated in a prenatal cohort established between 2014 and 2015 in Wuhan. Prenatal TCS exposure was measured in a complete series of urine samples collected at the first, second and third trimesters. General linear models and generalized estimating equation models were applied to evaluate the associations of the averaged maternal urinary concentrations of TCS over trimesters and trimester-specific urinary TCS with the *z*-scores of estimated fetal weight, head circumference, abdominal circumference, and femur length at 16, 24, and 31 gestational weeks, weight and length at birth, and weight and height at 0.5, 1, and 2 years of age.

Results: In overall infants, we did not observe any significant association of the averaged maternal urinary concentrations of TCS over trimesters with ultrasound parameters and size at birth. However, a positive association of borderline statistical significance was found between averaged prenatal TCS exposure and the third-trimester estimated fetal weight *z*-score in girls in sex-stratified analyses (β = 0.054, 95% CI: −0.005, 0.113, $p = 0.07$). Moreover, averaged prenatal TCS exposure was positively associated with 2 year-old weight *z*-score among total infants (β = 0.046, 95% CI: 0.005, 0.087). After stratifying by sex, the same association was observed in girls with more prominent estimation (β = 0.062, 95% CI: 0.000, 0.124), whereas the association weakened and became not significant in boys (β = 0.033, 95% CI: −0.024, 0.089). TCS exposure at 1st and 2nd-trimester were positively associated with weight *z*-score at 2 years, in both overall and female infants.

Conclusions: Prenatal exposure to triclosan was associated with elevated third-trimester estimated fetal weight and 2 year-old weight *z*-score in girls, and the early and middle stage of pregnancy may be the windows of vulnerability. Apart from these findings, we did not find strong evidence for prenatal triclosan exposure in relation to fetal and early-childhood growth.

* Correspondence to: S. Xu, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan 430030, People's Republic of China.
** Correspondence to: Z. Cai, Department of Chemistry, Hong Kong Baptist University, Hong Kong, SAR, People's Republic of China.
E-mail addresses: zwcai@hkbu.edu.hk (Z. Cai), xust@hust.edu.cn (S. Xu).
[1] Both authors contributed equally to this work.

https://doi.org/10.1016/j.envint.2018.07.022
Received 13 March 2018; Received in revised form 10 July 2018; Accepted 14 July 2018

1. Introduction

Triclosan (TCS) is a synthetic broad-spectrum antimicrobial agent produced and incorporated into numerous personal care products with which we come into contact in daily life, such as toothpaste, mouthwash and soaps (Calafat et al., 2008; Liao and Kannan, 2014). The consumption of personal care products leads to wide TCS exposure in the general population, mainly through ingestion and dermal absorption (Moss et al., 2000; Sandborgh-Englund et al., 2006; Scinicariello and Buser, 2016). Exposure to TCS is also widespread among susceptible individuals such as pregnant women in China (Ding et al., 2017; Huo et al., 2018) and other countries worldwide (Arbuckle et al., 2015; Meeker et al., 2013; Philippat et al., 2014; Wolff et al., 2008), with detectable concentrations of TCS in maternal urine (Calafat et al., 2008), maternal blood (Shekhar et al., 2017), amniotic fluid (Philippat et al., 2013), and cord blood (Pycke et al., 2014). The detectable concentrations of TCS in amniotic fluid and cord blood indicate that TCS can cross the placenta barrier to enter the fetal environment, and thus probably influence the developing fetus because of its endocrine disrupting properties (Dann and Hontela, 2011; Philippat et al., 2013; Pycke et al., 2014).

Fetal development is perceived as a particularly sensitive and vulnerable period for exposure to endocrine disrupting chemicals since hormonal imbalance during this particular stage may cause irreversible consequences (Buckley et al., 2016; Vuong et al., 2016). In experimental animal studies, exposure to TCS during pregnancy may result in spontaneous abortion, reduce live birth rate, lower gravid uterine weight, impair thyroid homeostasis, and delay female pubertal development in offspring (Feng et al., 2016; Rodriguez and Sanchez, 2010).

Several epidemiological studies have investigated the association of prenatal exposure to TCS with birth outcomes and the results still remain ambiguous (Ding et al., 2017; Geer et al., 2017; Huo et al., 2018; Lassen et al., 2016; Philippat et al., 2012; Wolff et al., 2008). Majority of the studies have determined TCS in urine or blood in one spot sample collected during pregnancy and did not highlight any significant relationships between maternal urinary concentrations of TCS and birth outcomes (Ding et al., 2017; Geer et al., 2017; Huo et al., 2018; Philippat et al., 2012; Wolff et al., 2008). However, Lassen et al. observed a significant positive association between single spot urine measures of TCS during pregnancy and birth length in male infants from Denmark (Lassen et al., 2016). Only one study, also utilizing single spot urine samples, investigated the associations between maternal urinary concentrations of TCS and anthropometric measures started from the intra-uterine period to 3 years of age in French male newborns and reported a significant negative association between maternal urinary TCS and estimated fetal weight, whereas observed suggestive positive association with weight measured from birth to 3 years (Philippat et al., 2014). Recently, Ferguson et al. assessed prenatal TCS exposure in incomplete urine samples from three time points during pregnancy and observed a suggestive negative association of prenatal exposure to TCS with birth weight *z*-score only in male infants from Boston (Ferguson et al., 2017). Another study conducted in 213 American newborns reported that prenatal TCS exposure, which was also assessed in incomplete urine samples from three time points during pregnancy, was associated with decreased birth weight in overall infants (Messerlian et al., 2018). None of the above-mentioned studies have combined repeated measurements of TCS in a complete series of three urine samples from pregnant women and multiple anthropometric measurements started from the intra-uterine period to early childhood.

Due to the relatively short half-life of TCS (about 11 h) in the human body (Sandborgh-Englund et al., 2006), repeated measurements of urinary TCS over trimesters may accurately estimate the average exposure during the whole gestation (Philippat et al., 2012). The aim of our study was to examine the associations of maternal urinary excretion of TCS (Calafat et al., 2008) in urine samples collected at the first, second, and third trimesters in 850 pregnant women as a measure of prenatal TCS exposure with ultrasound parameters (*z*-scores of estimated fetal weight, head circumference, abdominal circumference, and femur length) and birth size (birth weight and birth length *z*-score) as well as early-childhood growth (weight, height *z*-scores at 6 months, 1 year and 2 years).

2. Materials and methods

2.1. Study population

This study was conducted at a major maternity hospital named Women and Children Medical and Healthcare Center of Wuhan, in central China, between March 2014 and March 2015. Newly pregnant women with an 8–16 weeks singleton gestation (confirmed through ultrasound examination), residing in Wuhan city and coming for their first antenatal care visit were invited to participate in the study, with the willingness to donate their urine samples during regular antenatal examinations and give birth at the study hospital. Infants were enrolled at birth and invited to return to the children's healthcare department at the study hospital for follow-up visit at 6 months, 1 year, and 2 years. Based on the availability of urine samples, a subset of women (n = 856) who had a complete series of urine samples at the first (13.0 ± 1.1 weeks, n = 856), second (23.6 ± 3.2 weeks, n = 856) and third trimesters (35.9 ± 3.4 weeks, n = 856) of pregnancy were selected in the present study and measured for urinary TCS concentrations. Of the 856 mother-infant pairs, 6 participants were excluded because of neonatal birth defects (n = 5) and active maternal smoking during pregnancy (n = 1), whereas none of the participants were alcohol users, leaving 850 mother-infant pairs eligible for analyses. We did not specifically choose non-smokers and non-alcohol users in the present study. The number of pregnant women who reported smoking and drinking was small, because it is rare for Chinese women to smoke and drink. Since adjustment for smoking and drinking would not make sense in our study due to small numbers, we deleted the only one woman who remained an active smoker during pregnancy. All pregnant women in this study received a detailed explanation and provided written informed consent at enrollment. The study was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology, and the study hospital.

2.2. Prenatal triclosan exposure assessment

At the first, second, and third trimester of gestation, maternal urine samples were collected during routine antenatal visits to the hospital and were subsequently divided into aliquots in polypropylene containers and immediately stored at −20 °C until further analysis for TCS.

Urinary TCS was measured by ultra-high performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS), as in our previous study detailed by Zhao et al. (Zhao et al., 2017). In brief, 1 mL of urine sample was used for the extraction of TCS by liquid–liquid extraction method. The total supernatant collected in three time extraction procedure was concentrated to near-dryness under a gentle nitrogen gas flow and reconstituted with 200 μL of acetonitrile-water (6:4). The solution was further centrifuged and 150 μL supernatant were finally transferred into a glass vial for analysis.

The detection of urinary TCS concentrations was achieved with a Ultimate 3000 UPLC system (Dionex, Sunnyvale, CA, USA), interfaced with a Thermo Scientific™ TSQ Quantiva™ Triple Quadrupole mass spectrometer (negative-ion electrospray ionization mass spectrometry and multiple reaction monitoring mode, Thermo Scientific, San Jose, CA), with the isotope-labeled internal standard. Five microliters of the extract was injected and the chromatographic separation was accomplished on Thermo Scientific Betasil C_{18} column (2.1 mm × 100 mm, 3 μm) with ultrapure water and acetonitrile served as mobile phase gradients. Procedural blanks and quality control samples were included in each batch of samples. The present method showed satisfactory