Environmental Pollution 238 (2018) 717–724

Contents lists available at ScienceDirect

Environmental Pollution

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

Relationship between maternal exposure to bisphenol S and pregnancy duration☆

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ARTICLE INFO

Article history:
Received 22 November 2017
Received in revised form
16 March 2018
Accepted 16 March 2018

Keywords:
Bisphenol S
Urine
Gestational age
Pregnancy duration
Birth weight

ABSTRACT

Bisphenol S (BPS) has been progressively used due to the potential safety problems of bisphenol A (BPA). Thus Human studies are needed to investigate the developmental effects of BPS. In this study, the impact of maternal BPS exposure on birth outcomes was evaluated with linear and logistic regression models. BPS was analyzed in spot urine samples collected from 985 pregnant women at admission to labor. It was found in 93.7% of the urine samples with the specific gravity adjusted geometric mean concentration of 0.17 μg/L. One ln-unit increase in urinary BPS was associated with a 0.72-day increase in pregnancy duration (95% CI: 0.34, 1.09). When stratified by fetal sex, each ln-unit increase in maternal urinary BPS was significantly correlated with increased gestational age [adjusted β = 1.02, 95% confidence intervals (CI): 0.47, 1.57] and increased odds of late term birth [adjusted odds ratio = 1.29, 95% CI: 1.00, 1.67] for girls, but not significantly for boys. Including maternal urinary BPA and BPS in one model did not change the results. Associations of BPS with birth weight or length were not observed. This is the first report about BPS exposure for pregnant women from China. Higher maternal urinary BPS concentrations were associated with increased gestational age, suggesting maternal BPS exposure may interfere with pregnancy duration. The findings require replication but reveal the probable risks posed by the developmental BPS exposure.

1. Introduction

Bisphenol S (BPS) is a main alternative of bisphenol A (BPA) in the production of polycarbonate plastics and epoxy resins (Chen et al., 2016; Wu et al., 2018). The toxicity of BPA has been intensively investigated previously, and its exposure has been linked to numerous adverse health outcomes, particularly among infants and young children (Braun and Hauser, 2011). As a result, BPA usage in some consumer products was banned in many countries (European Commission, 2011; Health Canada, 2009; U.S. FDA, 2014); instead, BPS has been increasingly applied (Liao et al., 2012a; Rochester and Bolden, 2015).

BPS was regarded as a "safe" alternative to BPA because of its greater stability against high temperature and resistance to sunlight than BPA, though BPS still leaches from food cans and containers (Viñas et al., 2010). This chemical has been widely detected

☆ This paper has been recommended for acceptance by Payam Dadvand.
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https://doi.org/10.1016/j.envpol.2018.03.057
0269-7491/

in foodstuffs (Liao and Kannan, 2013), personal care products (Liao and Kannan, 2014), clothes (Xue et al., 2017), and paper products (Bjornsdotter et al., 2017; Liao et al., 2012b). BPS has also been found in dust (Liao et al., 2012c), water (Yamazaki et al., 2015; Yang et al., 2014b), sediment (Song et al., 2014), and sludge (Sun et al., 2017; Yu et al., 2015). Inevitably, widespread human exposure to BPS has occurred (Heffernan et al., 2016; Liao et al., 2012a; Liu et al., 2017).

Current knowledge on the health impact of BPS is limited. No previous epidemiological study has explored the developmental effects of BPS. *In vitro* studies have shown that BPS can bind to estrogen receptors (ER) and drive estrogen-induced gene transcription even at physiologically relevant concentrations (Grignard et al., 2012; Hashimoto et al., 2001; Kitamura et al., 2005; Viñas and Watson, 2013). Studies in zebrafish have shown that parental BPS exposure altered the homeostasis of sex steroid hormones and disrupted reproduction or development (including increased hatch time) (Ji et al., 2013; Kinch et al., 2015; Naderi et al., 2014; Qiu et al., 2016). Furthermore, evidence shows that BPS exhibits the effect of increasing the synthesis of progesterone which is a key hormone for maintenance of pregnancy and control of human parturition (Rosenmai et al., 2014).

Recent data have shown that human exposure level of BPS was on the rise (Ye et al., 2015). Considering the unique vulnerability of pregnant women and their offspring, it is worthwhile to obtain data about BPS exposure levels in this population and assess the developmental risks posed by this chemical. Therefore, in this study, BPS exposure was measured in urine samples from pregnant women in China, and its association with birth outcomes was examined.

2. Materials and methods

2.1. Study population

The population in the present study was selected from pregnant women participating in the Healthy Baby Cohort (HBC), China, focusing on environmental exposures and mother-infant health. A detailed report on the HBC has been introduced previously (Xia et al., 2016). In brief, this birth cohort has recruited 11,311 pregnant women who delivered live singleton newborns at Women and Children Medical and Healthcare Center of Wuhan from September 2012 to October 2014. The protocol was approved by ethics committees as described previously (Xia et al., 2016). All women gave signed informed consent. Urine samples ($n = 990$) collected before delivery were chosen randomly among participants recruited in 2014 for BPS and BPA determination. After excluding mothers who delivered an infant with a birth defect ($n = 5$), 985 mother-infant pairs were included. The mother-infant pairs in this study presented similar general characteristics to the population in HBC (Supplementary materials, Table S1).

2.2. Birth outcomes and data collection

Newborn weight (g), length (cm), and gestational age (days) at birth were obtained from the medical birth records. Birth length and weight of infants were measured less than 1 h after delivery by skilled nurses following standardized procedures. All the pregnant women in this study had first-trimester ultrasound examinations. The gestational age was estimated by first-trimester ultrasound data, which is more objective than self-reported last menstrual period (Savitz et al., 2002). Preterm delivery was a delivery before 37 weeks gestational age. Late term was a delivery with 41 0/7–41 6/7 weeks of gestation according to American College of Obstetricians and Gynecologists and the Society (ACOG, 2013). Small for gestational age (SGA) was identified as a birth weight below the 10th percentile compared with the distribution of birth weight in the same gestation week and sex (Mikolajczyk et al., 2011) based on data from all the newborns in the HBC.

Covariates information (socio-demographic characteristics, health behavior, etc.) was obtained during in-person interviews by trained nurses. The body mass index (BMI) during pre-pregnancy was estimated by self-reported data of height and weight. Information on medical history and infant sex were obtained from the medical records.

2.3. Sample collection and urinary BPS measurement

Pregnant women offered spot urine samples immediately after they were admitted into hospital in preparation for delivery. The median of the gestational age at sampling was 39.0 weeks (range: 32.0–42.0 weeks). Urine samples were stored at −20 °C in polypropylene tubes.

Ultra-high performance liquid chromatography and triple quadrupole mass spectrometry (UPLC-MS/MS, Waters, MA, USA) were applied to measure the concentrations of urinary BPS with minor modifications (Xue et al., 2015). Briefly, 20 μL of methanol containing 200 μg/L of internal standard $^{13}C_{12}$-BPS (98%, CLM-9319, Cambridge Isotope Laboratories, Andover, MA, USA) was mixed with 1 mL of urine sample. The sample was then incubated with 10 μL of β-glucuronidase/sulfatase (G0876, Sigma, St. Louis, MO, USA) and 200 μL ammonium acetate (pH = 5.0) at 37 °C overnight. After the deconjugation, sample extraction was repeated 3 times with 3 mL of methyl tert-butyl ether/ethyl acetate (5:1, v/v). The supernatant was concentrated in a glass tube under a gentle nitrogen stream. The residue was then dissolved with 0.5 mL of acetonitrile/water (6:4, v/v) and filtered for analysis with UPLC-MS/MS. BPA (internal standard: $^{13}C_{12}$-BPA, Sigma, St. Louis, MO, USA) was simultaneously measured in each urine sample. Because the primary metabolite of BPS is BPS-glucuronide (Skledar et al., 2016; Song et al., 2017), the glucuronidase deconjugation was performed, and then free plus conjugated BPS was quantified. The efficiency of deconjugation was identified by deconjugation of purchased bisphenol A-β-Glucuronide (final concentration 100 μg/L, Catalogue number: B519510, Toronto Research Chemicals, Toronto, Ontario, Canada) every week during the analyses.

The limit of quantitation (LOQ) for BPS and BPA was 0.02 μg/L and 0.50 μg/L, separately, defined as the lowest point of the calibration standard with a signal-to-noise ratio of $>= 10$, with a $r >= 0.994$ calibration curve (Xue et al., 2015). Every batch contained one procedural blank, one duplicate, one matrix spike sample and thirty urine samples. BPA and BPS found in procedural blanks were subtracted from measured sample values. BPS was detected with about 0.006 μg/L in 30% batches of procedural blanks, and BPA was detected with about 0.15 μg/L in all batches. The relative recoveries spiked into each sample were in the range of 85–115% for BPA, and 89–105% for BPS.

The BPA and BPS concentration was corrected for the urinary specific gravity (SG) (Cantonwine et al., 2015). SG was measured at room temperature by a refractometer (Atago PAL-10S, Atago, Tokyo, Japan).

2.4. Data analysis

Urine samples with concentrations less than LOQ were imputed with LOQ divided by the square root of 2. Urinary concentrations of BPS, which were skewed to the right, were transformed using natural logarithm (ln). Differences in distributions of ln-transformed urinary bisphenol analogue concentrations in term of the participant characteristics were analyzed by one-way