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Associations between repeated measures of maternal urinary phthalate metabolites during pregnancy and cord blood glucocorticoids

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ABSTRACT

Background: Previous studies have suggested that phthalates might disrupt fetal steroidogenesis. However, the evidence of the effects of prenatal phthalate exposure across pregnancy on fetal glucocorticoids was insufficient.
Objective: We investigated the associations between urinary phthalate metabolites across pregnancy and cord blood glucocorticoids in a prospective birth cohort.
Methods: Our study included 553 mother-infant pairs from a prospective birth cohort conducted in Wuhan, China. Maternal urine samples were collected at 14, 24 and 36 weeks of gestation (mean). Urinary phthalate metabolites and cord blood glucocorticoids (cortisol and cortisone) were measured. Generalized estimating equation models were conducted to explore the relationships of phthalate metabolite concentrations at each trimester and glucocorticoid levels.
Results: Among the participants, mono-benzyl phthalate (MBzP) in the first trimester was associated with higher cortisol/cortisone ratio concentrations, and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) measured in the third trimester were associated with decreased cortisone. Moreover, the associations between phthalates and glucocorticoids varied by sex. Among the female infants, each 10-fold increase in several maternal urinary phthalate metabolite concentrations in 1st and 3rd trimester was associated with the increased glucocorticoid levels with percent changes ranged from 16.2%–55.9%. However, among male infants, each 10-fold increase in maternal urinary MECPP, mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and MEOHP in 3rd trimester was associated with 20.8%–36.3% decreased cortisol and cortisone levels, respectively.
Conclusion: We have shown that prenatal phthalate exposure during early and late trimester disrupted the infant steroidogenesis and these associations might be modified by infant sex. To the best of our knowledge, this is the first study to evaluate phthalate exposure at three trimesters during pregnancy in relation to infant glucocorticoids.

1. Introduction

Glucocorticoids, including cortisol and its metabolite cortisone, play an integral role in regulating the homeostasis in metabolism and growth, especially for the maturation of the fetal brain and lungs (Moisiadis and Matthews, 2014). Cortisol in fetal circulation may be originated from the maternal adrenal gland during whole pregnancy, as well as from the fetal adrenal gland as early as week 8 of gestation (Murphy et al., 2006; Goto et al., 2006). The respective contribution of the mother or the fetus to the production of glucocorticoid hormones remains unclear. However, it is well known that cortisol in cord blood is much lower than that in maternal blood, owing to the barrier enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) in the placenta which can metabolize cortisol to its inactive metabolite cortisone (Fowden et al., 2016). Glucocorticoids levels in umbilical cord blood, an indicator of the fetal stress response (Gitau et al., 2001), may be affected

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by maternal or fetal characteristics including gestational age and infant sex (Giesbrecht et al., 2016; Rog-Zielinska et al., 2014). Human health data have shown that insufficient or excess glucocorticoid in fetal development may have an impact on gene methylation and histone modification, which can exert long-lasting adverse effects on the cardiovascular system in later life (Wood, 2013). Previous studies have also reported that an elevated ratio of cortisol to cortisone, reflected the decreased activity of 11β-HSD2, might allow an increased access of maternal glucocorticoids to the fetus, further retard growth and lead to higher offspring systolic blood pressure (Huh et al., 2008). Therefore, maintaining fetal intra-uterine glucocorticoid homeostasis is critical for fetal development in later life.

Fetal hormone system homeostasis might be susceptible to early life endocrine disrupting chemicals exposure, such as phthalates (Scott et al., 2009). Phthalates, a kind of synthesized plasticizer, have been widely used in industry and consumer products, such as plasticizer, adhesives, food packaging plastics and personal care products (ATSDR, 2002). Because of the weak affinity towards other mixed substances, phthalates can easily leach from products into the environmental media. Phthalates have been widely measured in pregnant women all over the world (Cantonwine et al., 2014; Myridakis et al., 2015; Watkins et al., 2017a, 2017b; Zhu et al., 2016). Recently, prenatal phthalate exposure has been associated with some adverse effects, such as decreased (Zhang et al., 2018) birth weight, altered anogenital distance (Wenzel et al., 2018) and impaired children neurodevelopment (Kim et al., 2011; Whyatt et al., 2012) in the previous studies. The potential mechanisms of these toxicological effects on fetal growth might be due to the fact that phthalates might alter hormone system homeostasis through binding with some receptors which were related to fetal development, such as glucocorticoid and peroxisome proliferator-activated receptors (Sathyanarayana et al., 2017; Adibi et al., 2017; Hong et al., 2009).

Experiments *in vitro* have shown that phthalate inhibited rat and mouse 11β-HSD2 activities, indicating the possible disruption effects of phthalate exposure on glucocorticoids (Zhao et al., 2010; Hong et al., 2009). To date, only two human studies reported the association between prenatal phthalate exposure and glucocorticoid levels in the literature. Recently, Araki et al. reported an inverse association between maternal blood mono-2-ethylhexyl phthalate (MEHP) levels at 23–35 weeks of gestation, with cord blood cortisol and cortisone in a prospective birth cohort (Araki et al., 2017). However, Jensen et al. reported a positive association between amniotic fluid mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) and cortisol levels at the 2nd trimester in a population including cryptorchidism and hypospadias cases and controls (Jensen et al., 2015). Both of these findings have suggested that prenatal phthalate exposure might disrupt the regulation glucocorticoid metabolism in the fetus. However, these studies have focused on only a specific group of phthalate metabolites and used one-spot samples during pregnancy. The variations of phthalate during pregnancy raised a concern that a single spot sample might not be adequate to assess prenatal phthalate exposure (Braun et al., 2012).

Thus, in the present work, we analyzed maternal urinary nine phthalate metabolites during 1st, 2nd and 3rd trimesters and cord blood glucocorticoids, and applied generalized estimating equation model to explore the relationships between prenatal phthalate exposure and infant glucocorticoids in a prospective birth cohort. To the best of our knowledge, this is the first study to investigate phthalate exposure at three trimester during pregnancy in relation to infant glucocorticoids.

2. Methods

2.1. Study population and data collection

The participants in this study were selected between 2014 and 2015 at Wuhan Women and Children Medical Care Center, a major maternity hospital in Wuhan, China. Study inclusion criteria were shown as follows: (1) residents of the Wuhan; (2) a singleton gestation with < 16 weeks pregnant at enrollment; (3) willing to have prenatal care and give birth in the study hospital. There were 856 participants who have donated urine samples at 1st, 2nd and 3rd trimester. A total of 610 cord blood samples were available for glucocorticoid measurements. Mothers (n = 57) who had pregnancy-induced hypertension or gestational diabetes mellitus were excluded from the analysis. Finally, 553 participants were included in the final analysis. All participants signed informed consents and registered in this cohort for enrollment. Ethical permission was taken from the ethics committees of the Women and Children Medical and Healthcare Center of Wuhan and Tongji Medical College, Huazhong University of Science and Technology.

We conducted face-to-face interviews with the participants to gather maternal demographic and socioeconomic characteristics (such as maternal age, ethnicity, and education) and life style in the pregnancy (alcohol consumption and smoking). The gestational age (calculated based on the last menstrual period) at birth, mode of delivery, as well as the infants' birth date, gender, and birth weight were obtained from medical records. The maternal pre-pregnancy body mass index (BMI) was computed by pre-pregnancy weight (extracted from the first prenatal visit records in the hospital) and height (measured with a stadiometer).

Table 1
Characteristics of the included (n = 553) and total (n = 856) mother-infant pairs [n (%)].

Characteristics	Included	Total
Age (years)		
18–24	97 (17.5)	124 (14.5)
25–29	290 (52.5)	451 (52.7)
30–34	140 (25.3)	227 (26.5)
≥35	26 (4.7)	54 (6.3)
Mean (± SD)	28.3 ± 3.2	28.6 ± 3.3
Pre-pregnancy BMI (kg/m^2)		
Normal (18.5–23.9)	383 (69.3)	584 (68.2)
Underweight (< 18.5)	111 (20.1)	157 (18.3)
Overweight (≥24)	59 (10.6)	115 (13.4)
Mean (± SD)	20.7 ± 2.7	20.9 ± 2.8
Parity		
1	472 (85.4)	736 (86.0)
≥2	81 (14.6)	120 (14.0)
Educational level		
More than high school	456 (82.5)	671 (78.4)
High school and below	97 (17.5)	185 (21.6)
Alcohol consumption during pregnancy		
No	553 (100.0)	856 (100.0)
Yes	0 (0.0)	0 (0.0)
Smoking during pregnancy		
No	552 (99.8)	855 (99.9)
Yes	1 (0.2)	1 (0.1)
Passive smoking during pregnancy		
No	371 (67.1)	570 (66.6)
Yes	182 (32.9)	286 (33.4)
Mode of delivery		
Vaginal delivery	236 (42.7)	331 (38.7)
Cesarean delivery	317 (57.3)	525 (61.3)
Fetal sex		
Male	280 (50.7)	447 (52.2)
Female	272 (49.3)	409 (47.8)
Gestational age (week)		
Mean (± SD)	39.4 ± 1.1	39.4 ± 1.2
Birth weight (g)		
Mean (± SD)	3330.4 ± 399.3	3316.8 ± 409.2

Abbreviations: BMI, body mass index; SD, standard deviation.

2.2. Phthalate metabolites measurement

Maternal urine samples were collected in polypropylene tubes at first trimester (13.1 ± 1.2 weeks), second trimester (23.6 ± 3.3 weeks) and third trimester (36.0 ± 3.3 weeks) and were

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