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Maternal phthalate exposure during early pregnancy and at delivery in relation to gestational age and size at birth: A preliminary analysis

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Abstract

Epidemiologic studies of *in utero* phthalate exposure and birth outcomes have had conflicting findings. The objective of this study was to characterize maternal phthalate exposure across pregnancy, examine associations between maternal phthalate levels and infant size and gestational age at birth, and investigate relationships between concurrent bisphenol A (BPA) and phthalate exposure and birth outcomes. Women in the Michigan Mother-Infant Pairs cohort provided urine and blood samples during their first trimester and at delivery. Urinary phthalate metabolites and serum BPA were measured at both time points, and birth weight, length, head circumference, and gestational age were recorded from medical records. Maternal DEHP metabolite concentrations were significantly higher at delivery compared to the first trimester ($p<0.05$), suggesting increased DEHP exposure late in pregnancy. A number of phthalate metabolites were associated with birth size and gestational age in patterns that varied by sex and timing of exposure, independent of BPA exposure.

Keywords

phthalates; bisphenol A; *in utero*; exposure; birth weight; gestational age

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1. Introduction

Phthalates are a class of endocrine disrupting chemicals (EDCs) that are widely used in a variety of consumer products (1) and are common contaminants in food (2). As a result, human exposure to phthalates is ubiquitous (3), generating concern regarding potential exposure-related health effects. Exposure to phthalates and other EDCs during pregnancy is of particular concern because hormonal disruption during fetal development may influence fetal growth (4), with potential long-term effects on health (5). In human studies, maternal phthalate concentrations during pregnancy have been associated with alterations in hormones that play key roles in pregnancy maintenance and fetal growth and development (6), such as testosterone (7), progesterone (8), and thyroid hormone (8,9). In addition, animal and *in vitro* studies have demonstrated that phthalates and their metabolites are both anti-androgenic (10) and weakly estrogenic (11). Because many hormones play distinct roles in male and female fetal development, these findings provide the basis for examining sex-specific relationships between *in utero* phthalate exposure and birth outcomes.

Previous epidemiologic studies evaluating associations between *in utero* phthalate exposure and size at birth have had conflicting findings, possibly due to methodological differences in study design, exposure assessment, and study population. A number of studies reported associations, often in sex-specific patterns, between markers of *in utero* phthalate exposure with both decreased (12,13) and increased birth weight (14), and increased head circumference (15), while others found no association between *in utero* exposure and birth size (16,17). A recent review describes these studies in detail (6). In addition, a meta-analysis of data from three birth cohorts found that maternal urinary mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP) concentrations in second and third trimesters were associated with lower birth weight, while mono-oxo-isononyl phthalate (MOiNP) was marginally associated with higher birth weight, after adjustment for other environmental exposures and covariates (18). Previous studies have also reported associations of *in utero* phthalate metabolites with decreased gestational age at birth (19,20) and increased risk of preterm birth (<37 weeks) (21-23); although, increased gestational age has also been reported in relation to maternal urinary monomethyl (MMP), monoethyl (MEP), and monobutyl (MBP) phthalates (15), and di-2-ethylhexyl phthalate (DEHP) metabolites (24).

However, many of these studies evaluated phthalate exposure at one point in time, usually late in pregnancy. Maternal urinary phthalate metabolite concentrations vary across pregnancy, such that levels measured late in pregnancy do not reflect exposure during earlier trimesters (22,25,26). As a result, previous studies that only measured phthalate metabolites during the third trimester could not evaluate relationships between exposure during early critical windows of organ differentiation, and birth outcomes. One study measured phthalate metabolites in one urine sample per participant collected between 6 to 30 weeks of gestation, potentially leading to misclassification of exposure if there are specific critical windows of exposure vulnerability during pregnancy (16). Another study measured parent phthalate concentrations in blood and meconium samples rather than urinary metabolites, which are less vulnerable to contamination (12).

The objectives of this study were to characterize maternal urinary phthalate metabolite concentrations during the first trimester and at delivery among mothers in an ongoing Michigan birth cohort, and to investigate associations between maternal phthalate levels during pregnancy and infant size and gestational age at birth. In addition, because we recently found associations between first trimester maternal plasma bisphenol A (BPA) concentrations and lower birth weight in female offspring within this same study population (27), we aimed to investigate relationships between co-exposure to BPA and phthalates during pregnancy and birth outcomes.

2. Material and Methods

2.1 Study Population

Women were recruited between 2009 and 2012 during their first trimester of pregnancy as part of the Michigan Mother-Infant Pairs (MMIP) project, an ongoing birth cohort. Women were informed of the study during their first prenatal visit at a University of Michigan OG/GYN facility, and were eligible to participate if they were 18 years of age or older, conceived naturally, and had a singleton pregnancy. Women provided spot urine and venous blood samples during their first trimester prenatal visit (8-14 weeks) and upon arrival at the hospital for delivery, prior to IV placement. The University of Michigan Medical School Institutional Review Board approved this study, and all women provided written informed consent prior to participation.

2.2 Phthalate Metabolite and BPA Measurement

Spot urine samples were collected into polypropylene urine collection containers, aliquoted into glass vials, and frozen at −80°C until analysis at NSF International (Ann Arbor, MI). Nine phthalate metabolites, comprising monoethyl phthalate (MEP), mono-*n*-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-3-carboxypropyl phthalate (MCPP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-carboxypentyl phthalate (MECPP), were measured at NSF International (Ann Arbor, MI) using isotope dilution–liquid chromatography–tandem mass spectrometry (ID–LC–MS/MS). This method is a slight modification of the Centers for Disease Control and Prevention (CDC) Laboratory procedure for urinary phthalate measurement and has been validated as previously described (28). The method accuracy (% nominal concentration) ranged from 88-107%, and the method precision (%relative standard deviation) ranged from 2-11% for individual phthalate metabolites. Summary measures for DEHP (ΣDEHP) and dibutyl phthalate (ΣDBP) metabolites for each sample were calculated by dividing individual metabolite concentrations by their molar mass and summing them. The ΣDEHP measure comprised MEHP, MEHHP, MEOHP, and MECPP, while the ΣDBP measure comprised MnBP and MiBP. Specific gravity (SG) was measured using a handheld digital refractometer (Atago Co., Ltd., Tokyo, Japan) at the time of sample analysis. Values below the limit of detection (LOD) were replaced with LOD/√2.

Plasma levels of unconjugated BPA (uBPA) and BPA glucuronide (gBPA) were previously measured following collection and analysis methods that were developed and validated by

four independent laboratories with the purpose of ensuring sensitive and accurate BPA quantification and minimal contamination (27,29). Relationships between these BPA measures and birth outcomes within the MMIP cohort (n=80, including 68 subjects in the present study) have been previously reported (27).

2.3 Outcome measures

Birth weight, birth length, head circumference, and gestational age were obtained from medical records. Birth weight was measured by nurses at delivery, while birth length and head circumference were measured the day after delivery. Individual providers determined whether the best estimate of gestational age presented in the medical record was based on last menstrual period (LMP) or ultrasound, as recommended by The American Congress of Obstetricians and Gynecologists (30).

2.4 Statistical Methods

Urinary phthalate metabolite and plasma BPA concentrations were log-normally distributed, and ln-transformed prior to regression analysis. To estimate overall phthalate exposure across pregnancy, first trimester and delivery concentrations were averaged for each phthalate metabolite. Phthalate concentrations were corrected for SG, a measure of urine dilution, using the following equation: $P_c=P[(SG_p-1)/(SG_i-1)]$ where P_c is the SG-corrected phthalate metabolite concentration (ng/mL), P is the measured phthalate metabolite concentration, SG_p is the median urinary SG (1.013), and SG_i is the individual's urinary SG. Spearman correlation coefficients were calculated to determine associations between first trimester and delivery phthalate metabolite concentrations, as well as between individual phthalate metabolites within each time period using SG-corrected concentrations. Intraclass correlation coefficients (ICCs) were calculated using random intercept mixed effect models to estimate between and within subject variability of log-transformed, SG-adjusted phthalate metabolite concentrations. ICCs are a measure of reliability of a measurement within an individual over time, with zero indicating no reproducibility and one indicating perfect reproducibility.

Linear regression was used to investigate associations between individual ln-transformed, SG-uncorrected phthalate metabolites (first trimester, delivery, or average) and birth outcomes. Child sex and maternal body mass index (BMI) were included as potential confounders, while urinary SG was included as a covariate to adjust for urine dilution. Gestational age was included in models predicting birth weight, length, and head circumference. Other covariates that were considered included maternal age, parity, income, and smoking status. In an effort to limit the number of covariates in our final models, these were not included as they were not associated with both exposure and outcome and did not substantially change phthalate effect estimates. Results are presented as the change in birth outcome (95% confidence interval) per interquartile range (IQR) increase in continuous phthalate metabolite.

In sensitivity analyses, sex-specific associations between phthalate metabolites and birth outcomes were investigated by entering a sex*metabolite interaction term into models, and when indicated, stratifying our results by child sex to obtain sex-specific effect estimates.

Based on our previously reported associations between maternal BPA levels during pregnancy and size and gestational age of offspring at birth (27), phthalate metabolite and BPA concentrations from the same time period (first trimester or delivery) were entered into regression models together to investigate relationships between co-exposure and birth outcomes. All analyses were performed using SAS version 9.4 (Cary, NC).

3. Results

3.1 Demographics and Phthalate Metabolite Distributions

Women in the present analysis represent 68 participants in the MMIP cohort study. On average, women were 31 years of age, white, married, slightly obese, non-smokers, and in their second pregnancy (Table 1). The average birth weight, length, and head circumference of the newborns were 3423g, 51.4cm, and 34.4cm, respectively. Although none of the infants in the study were clinically considered low birth weight (<2500g), two infants were born preterm.

Urinary phthalate metabolite distributions are shown in Table 2. Individual DEHP metabolites and ΣDEHP were significantly higher in samples collected at delivery compared to the first trimester ($p<0.01$). Phthalate metabolite concentrations measured during the first trimester were significantly correlated with one another (range: 0.34-0.99). Concentrations measured at delivery were similarly correlated, with the exception of DEHP metabolites, which were highly correlated with one another (range: 0.76-0.99), but less correlated with other phthalates (0.02-0.50) (Supplementary Data, Table S1). Most SG-corrected phthalate metabolites measured during the first trimester were not significantly correlated with concentrations at delivery, with the exception of MBzP ($r=0.35$, $p=0.003$) (Table 3). The reproducibility of urinary phthalate metabolite concentrations within individuals was low, with ICCs ranging from zero for DEHP metabolites to 0.32 for MBzP (Table 3).

3.2 Birth Outcomes in Males

A number of significant sex*phthalate interactions were observed, particularly for exposure during the first trimester (Supplementary Data, Table S2.), so model results are presented stratified by sex. Among males, specific phthalate metabolites measured at delivery were associated with larger size at birth after adjustment for SG, maternal BMI, and gestational age (Table 4). For example, an IQR increase in ΣDBP was associated with a 199g increase in birth weight (95%CI: 4.1, 393), while an IRQ increase in MCPP was associated with a 2.07cm increase in birth length (95%CI: 0.09, 4.06). When phthalate concentrations from the first trimester and delivery were averaged for each participant and entered into models as a measure of exposure over pregnancy, stronger associations between certain phthalates and birth size in males were observed. ΣDBP at the first trimester and at delivery were associated with a 191g and 199g increases in birthweight, respectively, but average ΣDBP over pregnancy was associated with a higher, significant 263g increase in birth weight (95%CI: 65.3, 461). Similarly, an IQR increase in average ΣDBP across pregnancy was associated with a 0.54cm increase in head circumference (95%CI: 0.00, 1.08), while associations with ΣDBP at the first trimester and delivery were smaller. Although not statistically significant,

all phthalate metabolites measured during the first trimester were associated with decreased gestational age at birth.

3.3 Birth Outcomes in Females

Among females, phthalate metabolites measured during the first trimester were also associated with non-statistically significant decreases in gestation age. In addition, an IQR increase in ΣDBP at delivery was associated with a 5.5 day decrease in gestational age (95%CI: −10.2, −0.8) (Table 5). After adjustment for gestational age and other covariates, associations between phthalate metabolites and size at birth varied by timing of exposure. An IQR increase in first trimester ΣDBP was associated with a 328g decrease in birth weight (95%CI: −621, −34.6), while the same increase at delivery was associated with a 1.67cm increase in birth length (95%CI: 0.04, 3.30). An IQR increase in first trimester MCPP was associated with a 1.79cm increase in birth length (95%CI: 0.40, 3.18), while the same increase at delivery was associated with 222g higher birth weight (95%CI: 10.5, 434) and 0.70cm larger head circumference (95%CI: 0.03, 1.38).

3.4 Concurrent BPA Exposure

Phthalate metabolite and BPA concentrations are not significantly correlated in this population (Supplementary Data, Table S1). When BPA and individual phthalate metabolites from the same time point (first trimester, delivery) were included together in models predicting birth outcomes, the observed associations between phthalate metabolites and birth outcomes did not materially change (Supplementary Data, Tables S3, S4).

4. Discussion

Maternal urinary phthalate metabolite concentrations measured during the first trimester of pregnancy were not correlated with levels measured at delivery, emphasizing the need for repeated phthalate measures during pregnancy to assess prenatal exposure. In addition, maternal DEHP metabolite concentrations were significantly higher at delivery compared to the first trimester, suggesting increased DEHP exposure late in pregnancy. A number of phthalate metabolites were associated with birth size and gestational age in patterns that varied by sex and timing of exposure.

4.1 Comparison with previous studies

Mothers in the present study had lower concentrations of most phthalate metabolites during the first trimester and at delivery compared to adult female NHANES participants during the same time period (2009-2012) (3). In addition, phthalate metabolite concentrations within the present study were lower than levels reported among pregnant women in Puerto Rico (25) and Spain (26). Correlations of first trimester and delivery metabolite concentrations were also slightly lower than previously reported correlations between first and third trimester concentrations among pregnant women in Spain (26).

The observed associations between maternal urinary MCPP (males), ΣDBP and MBzP (females) at delivery and increased birth length are consistent with a previous study, which reported associations between third trimester MBzP, MnBP, and MCPP and birth length

(15). However, the previous findings did not differ by newborn sex, while we observed significant interactions in relation to first trimester exposure. This suggests that sex-specific effects may occur earlier in fetal development. In addition, the observed relationships between DBP metabolites at delivery and decreased gestational age at birth among females is consistent with previously reported associations between maternal MnBP concentrations during pregnancy and increased risk of preterm birth (21-23). The observed associations between ΣDBP at delivery and increased birth weight among males is inconsistent with previously reported associations between DBP in cord blood and MBP in meconium and increased odds of low birth weight (12). However, among females in the present study, ΣDBP levels earlier in pregnancy were associated with decreased birth weight. In contrast to previous studies (13,18-20,24), DEHP metabolites measured during the first trimester or at delivery were not associated with size or gestational age at birth. Our findings are also inconsistent with a case-control study performed in France which found no significant associations between prenatal phthalate metabolite levels and birth outcomes (16), however, this study was different from the current analysis in many aspects, including study population, design, and standardization of phthalate levels that could potentially explain this discrepancy.

Previous animal studies have reported conflicting findings regarding *in utero* phthalate exposure and birth weight. For example, early rodent studies found that DEHP exposure was associated with decreased fetal and birth weight (31, 32]), while similar recent studies are consistent with our findings of no association (33, 34). Animal studies of *in utero* DBP exposure have also observed inconsistent effects on birth weight, with several studies reporting no effect (35-38), while others reported either decreased (39-41) or increased (42) birth weight. Interestingly, we observed differing relationships with measures of DBP exposure in the first trimester by sex, as exposure was associated with decreased birth weight in girls and increased birth weight in boys.

4.2 Timing of Exposure

The timing of urine sample collection likely played a role in both phthalate metabolite levels and their relationships with birth outcomes. First, DEHP metabolite concentrations at delivery were higher than in the first trimester, which is in contrast to previous studies that suggest average urinary phthalate concentrations typically stay the same or decrease across pregnancy (22,25,26). One explanation for this discrepancy could be that in the present study, women provided urine samples after arrival at the hospital for delivery, whereas women in previous studies often provided samples during their third trimester. The increase in DEHP metabolites at delivery could be due to an exposure related to beginning labor or hospital admittance. Although protocol dictated urine samples were collected prior to IV placement, a research coordinator was not present at the time of delivery, so the possibility of IV insertion prior to urine collection, and hence a potential source of DEHP exposure, cannot be ruled out. Dietary changes late in the third trimester may also lead to increased phthalate exposure during this time, but in this scenario we would also expect increased exposure to other phthalates often found in food. The strong correlation between DEHP metabolites and other phthalates during the first trimester but not at delivery also suggests a specific DEHP exposure associated with delivery in this study population. Increased DEHP

exposure, rather than sample contamination, is likely because we observed increases in the oxidative DEHP metabolites (MEHHP, MEOHP, and MECPP), which are only formed by *in vivo* enzymatic reactions.

We detected several significant associations between phthalate levels measured at delivery and birth size, but fewer associations with first trimester levels. Because phthalate metabolites measured at delivery are concurrent with birth outcome measures, reverse causation is possible. For example, an event may occur at delivery that leads to increased phthalate exposure, particularly among women with larger babies. However, in this scenario we would not expect to observe this association only among newborn girls, as phthalate exposure at delivery is not likely to depend on infant sex. In addition, birth outcomes were not associated with DEHP metabolite levels, the only phthalates that were significantly higher at delivery.

The decreased birth weight in association with first trimester DBP levels, and increased head circumference in association with first trimester MCPP suggest that early pregnancy may be an important window of vulnerability for these exposure-related effects, particularly in girls. In contrast, various associations among boys were stronger when average phthalate concentrations were considered relative to levels at either time point, such as the observed relationships between DBP metabolites and increased birth weight. These findings may suggest that DBP exposure throughout pregnancy is more important for select birth outcomes compared to exposure at any one time, or that the average concentration is less susceptible to random measurement error, and thus more representative of true exposure.

4.3 Potential Mechanisms

Phthalate exposure during *in utero* development may affect size and gestational age at birth through endocrine disruption. Phthalate metabolite concentrations during pregnancy have been associated with altered thyroid hormones (8,9), which are crucial in fetal development. Indeed, both hyper and hypothyroidism during pregnancy have been associated with increased risk of preterm birth and low birth weight (43,44). Maternal phthalate levels have also been associated with decreased progesterone during pregnancy (8), which is related to increased risk of spontaneous abortion and preterm birth (45,46). Phthalates may disrupt maternal estrogen (11), which plays a role in maintaining pregnancy, fetal organ development, and the timing of parturition (46,47), or decrease maternal testosterone (7), which has been associated with decreased birth weight, particularly among male newborns (48). As many of these hormones have sex-specific effects during fetal development, we might expect sex-specific relationships between maternal phthalate levels and size at birth. Select results from the current study are consistent with this hypothesis. For example, first trimester ∑DBP metabolites were associated with increased birth weight in boys and decreased birth weight in girls.

Phthalates may also affect fetal growth and gestational length through induction of oxidative stress. We recently reported associations between maternal phthalate levels during pregnancy and 8-hydroxydeoxyguanosine (OHdG), a marker of DNA oxidation, and 8-isoprostane, a marker of global oxidative stress (49). Increased oxidative stress during

pregnancy is a known risk factor for preeclampsia, impaired placentation, intrauterine growth restriction, preterm birth, and low birth weight (50,51).

Epigenetic changes are another mechanism by which *in utero* phthalate exposure may affect size and gestational age at birth (52). For example, a recent study reported sex-specific associations between first trimester maternal urinary phthalate levels and methylation changes in placental tissue of two genes related to embryonic and placental growth (53). Another recent study reported that associations between third trimester urinary phthalates and decreased birth weight were mediated by decreases in LINE-1 methylation in placental tissue (54).

4.4 BPA Models

Phthalate and BPA exposure among pregnant women have been associated with altered hormone levels (8,55,56), increased oxidative stress during pregnancy (49,57), and birth outcomes such as low birth weight (18,27) and decreased gestational age (20). However, entering concurrently measured phthalate metabolite and BPA levels into regression models together did not alter our results. In addition, concurrently measured BPA and phthalate levels were not significantly correlated, so we would not expect the observed associations with phthalates to be confounded by BPA exposure.

4.5 Limitations and Strengths

This analysis included a preliminary subset of an ongoing birth cohort, thus our sample size was relatively small, limiting our statistical power. As a result, the number of covariates that could be entered into models together was limited, particularly in sex-stratified and multiple exposure models. Because this was an exploratory analysis, we also made a large number of comparisons, increasing the likelihood of chance findings. In addition, the method of determining gestational age at birth was not consistent across participants, as individual providers determined whether their patient's medical record displayed gestational age based on LMP or ultrasound, as suggested by The American Congress of Obstetricians and Gynecologists (30). However, LMP-based measurements were used for the majority of participants, and we would not expect the physician's preference to be related to participant's phthalate exposure, limiting potential bias. Another limitation was the collection of urine samples at delivery, rather than before the initiation of labor. Although samples were primarily collected upon arrival at the hospital, occasionally samples were collected once participants were admitted to the hospital and assigned a room. In addition, because phthalate metabolite concentrations vary within individuals across pregnancy (22,25,26), maternal urinary levels measured only during the first trimester and at delivery are unlikely to fully characterize prenatal phthalate exposure.

A key strength of the present study is repeated measurements of maternal exposure to phthalates and BPA in both early and late pregnancy. These points in gestation represent two distinct periods of fetal development, which allowed examination of potential sensitive windows of vulnerability to EDC exposure and investigation of longitudinal changes in EDC exposure across pregnancy.

5. Conclusion

Findings from this study support previous reports of highly variable phthalate exposure across pregnancy within individuals, emphasizing the need for repeated phthalate measures during pregnancy to assess prenatal exposure. In addition, a number of associations between maternal phthalate exposure during pregnancy and infant size and gestational age at birth were observed, independent of co-exposure to BPA. These associations were particularly apparent for DBP, and varied by infant sex and timing of exposure. These findings should be confirmed in larger study populations with repeated phthalate measures across pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Maternal DEHP metabolite levels were higher at delivery compared to the 1st trimester.
- Associations between prenatal phthalate levels and birth size varied by child sex and exposure timing.
- Co-exposure to bisphenol-A did not alter relationships between maternal phthalate exposure and birth outcomes.

Table 1

Population Characteristics

	N	%	Mean	SD	Range	
Maternal Age (years)	68		31.7	4.6	22.0	42.0
Maternal BMI	65		30.5	5.7	22.5	51.4
Gravida	68		2.22	1.09	1	5
Parity	68		0.72	0.83	0	4
Birth Weight (g)	68		3423	552	1885	4575
Birth Length (cm)	62		51.4	2.90	41	56
Head Circumference (cm)	63		34.4	1.67	25.5	37
Gestational Age (weeks)	68		39.6	1.12	36	41.7
Marital Status (married)	51	75.0				
Race (white)	57	83.8				
Smoking Status (current) *	3 *	4.41				
Cesarean	12	17.7				
Infant Sex (male)	36	52.9				
Education *						
High School	14	20.6				
College	15	22.0				
Graduate School	31	45.6				
Missing	8	11.8				
Income (USD)						
<50,000	22	32.8				
50,000-100,000	25	37.3				
>100,000	20	29.8				

SD= standard deviation;

* smoking status missing for 15 participants, education missing for 8 participants.

Table 2

Distribution of urinary phthalate metabolites (μg/L) unadjusted for specific gravity among participants during their first trimester, at delivery, and the average of both time points (n=68).

					Percentiles					
	LOD	**%<LOD**	**GM**	**GSD**	**5th**	**25th**	**50th**	**75th**	**95th**	**Max**
First Trimester										
MEHP	1.0	29.4	2.02*	2.52	<1	<1	1.96	4.08	13.6	21.6
MEHHP	0.1	0	7.16*	2.96	1.24	3.44	7.17	14.1	51.9	90.3
MEOHP	0.1	0	3.47*	2.91	0.50	1.71	3.72	6.75	22.5	42.8
MECPP	0.2	0	8.04*	2.78	2.04	4.41	8.29	14.9	42.6	84.7
MBzP	0.2	1.5	3.00	3.49	0.36	1.29	3.56	7.65	19.5	35.6
MBP	0.5	2.9	6.42	3.18	0.61	3.35	8.12	14.5	29.6	78.8
MiBP	0.2	10.3	3.20	5.08	<0.2	1.80	3.78	10.2	37.7	195
MCPP	0.2	2.9	1.93	3.28	0.32	0.71	2.31	4.35	11.3	32.6
MEP	1.0	0	30.5	4.25	3.61	11.0	29.6	76.5	370	889
ΣDEHP (μM/L)			0.07*	2.71	0.01	0.04	0.07	0.14	0.44	0.75
ΣDBP (μM/L)			0.05	3.64	0.003	0.02	0.05	0.10	0.33	0.94
Delivery										
MEHP	1.0	26.5	4.45*	6.15	<1	<1	2.47	21.3	111	1100
MEHHP	0.1	0	14.7*	5.03	1.21	5.22	14.6	42.2	206	635
MEOHP	0.1	1.5	7.40*	4.72	0.70	2.86	7.72	18.0	104	241
MECPP	0.2	0	15.8*	4.05	1.50	6.44	18.5	37.6	163	272
MBzP	0.2	0	2.75	3.01	0.58	1.23	2.65	5.86	16.5	45.7
MBP	0.5	5.9	4.79	3.13	<0.5	2.36	5.20	12.2	22.7	43.5
MiBP	0.2	10.3	3.01	5.47	<0.2	0.90	3.18	7.92	57.1	256
MCPP	0.2	5.9	1.73	4.67	<0.2	0.67	1.29	4.83	30.6	272
MEP	1.0	2.9	21.3	4.75	2.41	6.96	22.6	60.6	282	768
ΣDEHP (μM/L)			0.16*	4.33	0.02	0.06	0.16	0.42	2.00	7.56
ΣDBP (μM/L)			0.04	3.76	0.004	0.02	0.04	0.10	0.29	1.20

	LOD	%<LOD	GM	GSD	Percentiles					
					5th	25th	50th	75th	95th	Max
Average										
MEHP	1.0		4.50	4.16	<1	1.61	3.07	12.3	57.6	550
MEHHP	0.1		15.2	3.06	2.82	6.66	12.8	29.1	105	318
MEOHP	0.1		7.38	2.99	1.23	3.62	6.57	14.0	53.6	121
MECPP	0.2		15.7	2.58	3.45	8.23	15.0	31.2	88.5	137
MBzP	0.2		3.54	2.63	0.71	1.74	3.44	6.96	18.8	25
MBP	0.5		7.32	2.11	1.87	4.62	7.99	12.0	20.7	51
MiBP	0.2		4.73	3.49	1.17	2.12	4.10	9.42	31.8	183
MCPP	0.2		2.57	3.15	0.46	1.08	2.44	4.42	22.5	141
MEP	1.0		38.5	3.33	6.41	14.4	35.6	108	258	465
ΣDEHP (μM/L)			0.15	2.91	0.04	0.07	0.13	0.29	1.02	3.78
ΣDBP (μM/L)			0.06	2.51	0.02	0.03	0.06	0.09	0.33	0.88

LOD=limit of detection, GM=geometric mean, GSD=geometric standard deviation

*Significant difference between urinary concentrations at first trimester and delivery ($p<0.05$)

Table 3

. Spearman correlation and intraclass correlation coefficients between urinary phthalate metabolite concentrations measured during the first trimester and at delivery, corrected for urinary specific gravity (n=68).

Correlations between 1st Trimester and Delivery Concentrations				
Phthalate metabolite	**r**	**(p-value)**	**ICC**	**(95% CI)**
MEHP	0.14	(0.26)	0	
MEHHP	−0.04	(0.72)	0	
MEOHP	−0.002	(0.99)	0	
MECPP	0.05	(0.71)	0	
MBzP	0.35	(0.003)	0.32	(0.15, 0.55)
MBP	0.17	(0.16)	0.13	(0.02, 0.54)
MIBP	0.24	(0.05)	0.26	(0.10, 0.53)
MCPP	0.02	(0.85)	0.05	(0.0002, 0.91)
MEP	0.22	(0.07)	0.18	(0.04, 0.51)
ΣDEHP	−0.02	(0.86)	0	
ΣDBP	0.21	(0.09)	0.20	(0.06, 0.51)

Table 4

Among males, change in outcome associated with an IQR increase in maternal urinary phthalate concentrations during their first trimester, at delivery, and the average of both time points, adjusted for urinary specific gravity, maternal BMI, and gestational age (except for models evaluating gestational age).

MALES	First Trimester		Delivery		Average	
	Δ/IQR	95% CI	Δ/IQR	95% CI	Δ/IQR	95% CI
birth weight (g)						
MBzP	152	(−150, 453)	150	(−71.1, 372)	181	(−72.8, 434)
MCPP	−274	(−558, 9.48)	178	(−103, 460)	−16.4	(−346, 313)
MEP	−119	(−363, 125)	104	(−140, 347)	52.2	(−229, 333)
ΣDEHP	−29.0	(−397, 339)	41.5	(−185, 268)	−2.32	(−229, 225)
ΣDBP	191	(−117, 500)	**199** *	**(4.06, 393)**	**263** *	**(65.3, 461)**
birth length (cm)						
MBzP	0.89	(−1.58, 3.37)	0.01	(−1.72, 1.74)	0.19	(−1.85, 2.23)
MCPP	−1.23	(−3.56, 1.10)	**2.07** *	**(0.09, 4.06)**	0.82	(−1.73, 3.36)
MEP	−0.55	(−2.49, 1.39)	−0.04	(−1.82, 1.74)	−0.77	(−2.83, 1.28)
ΣDEHP	0.60	(−4.32, 5.52)	0.03	(−1.59, 1.65)	−0.44	(−2.13, 1.25)
ΣDBP	0.88	(−1.65, 3.42)	0.89	(−0.59, 2.37)	1.23	(−0.36, 2.82)
head circumference (cm)						
MBzP	0.37	(−0.44, 1.19)	−0.16	(−0.78, 0.45)	0.01	(−0.72, 0.73)
MCPP	−0.36	(−1.14, 0.42)	0.58	(−0.16, 1.32)	0.51	(−0.39, 1.41)
MEP	0.06	(−0.58, 0.70)	0.01	(−0.63, 0.64)	0.17	(−0.58, 0.91)
ΣDEHP	0.08	(−1.55, 1.70)	−0.16	(−0.74, 0.42)	−0.22	(−0.83, 0.38)
ΣDBP	0.33	(−0.50, 1.15)	0.23	(−0.31, 0.77)	**0.54** *	**(0.00, 1.08)**
gestational age (days)						
MBzP	−1.66	(−7.27, 3.96)	0.66	(−3.23, 4.56)	0.27	(−4.35, 4.90)
MCPP	−2.39	(−7.84, 3.06)	2.87	(−1.84, 7.57)	0.82	(−4.98, 6.61)
MEP	−1.94	(−6.41, 2.54)	−0.83	(−5.03, 3.36)	−3.30	(−7.94, 1.34)
ΣDEHP	−1.36	(−8.14, 5.42)	0.91	(−2.94, 4.76)	−0.13	(−4.13, 3.86)
ΣDBP	−2.87	(−8.54, 2.80)	−0.68	(−4.23, 2.87)	0.09	(−3.81, 3.99)

* $p<0.05$.

Table 5

Among females, change in outcome associated with an IQR increase in maternal urinary phthalate concentrations during their first trimester, at delivery, and the average of both time points, adjusted for urinary specific gravity, maternal BMI, and gestational age (except for models evaluating gestational age).

FEMALES		First Trimester		Delivery		Phthalate Average	
		Δ/IQR	95% CI	Δ/IQR	95% CI	Δ/IQR	95% CI
birth weight (g)							
	MBzP	−149	(−554, 256)	270	(−59.0, 598)	43.8	(−311, 399)
	MCPP	272	(−36.2, 581)	**222** *	**(10.5, 434)**	164	(−25.3, 354)
	MEP	24.4	(−348, 396)	112	(−238, 462)	97.9	(−324, 520)
	ΣDEHP	−32.4	(−357, 292)	42.0	(−263, 348)	−35.7	(−334, 263)
	ΣDBP	**−328** *	**(−621, −34.6)**	112	(−256, 480)	−225	(−510, 60.5)
birth length (cm)							
	MBzP	0.30	(−1.62, 2.22)	**1.78** *	**(0.22, 3.34)**	0.65	(−1.02, 2.31)
	MCPP	**1.79** *	**(0.40, 3.18)**	0.78	(−0.26, 1.83)	0.69	(−0.21, 1.59)
	MEP	0.31	(−1.43, 2.06)	0.43	(−1.22, 2.08)	0.52	(−1.49, 2.52)
	ΣDEHP	0.36	(−1.14, 1.87)	−0.04	(−1.51, 1.42)	−0.34	(−1.75, 1.07)
	ΣDBP	−0.40	(−1.90, 1.11)	**1.67** *	**(0.04, 3.30)**	−0.01	(−1.42, 1.40)
head circumference (cm)							
	MBzP	0.29	(−1.00, 1.58)	0.86	(−0.24, 1.97)	0.24	(−0.89, 1.37)
	MCPP	0.09	(−0.97, 1.15)	**0.70** *	**(0.03, 1.38)**	0.37	(−0.24, 0.99)
	MEP	−0.55	(−1.70, 0.61)	0.15	(−0.97, 1.26)	−0.51	(−1.85, 0.83)
	ΣDEHP	0.23	(−0.78, 1.25)	0.42	(−0.55, 1.38)	0.31	(−0.64, 1.25)
	ΣDBP	0.26	(−0.76, 1.27)	−0.01	(−1.20, 1.18)	−0.07	(−1.02, 0.88)
gestational age (days)							
	MBzP	−0.75	(−6.96, 5.45)	−2. 08	(−7.28, 3.13)	−2.60	(−7.87, 2.67)
	MCPP	−0.02	(−4.99, 4.95)	−0.04	(−3.59, 3.50)	−0.11	(−3.20, 2.98)
	MEP	−1.93	(−7.48, 3.61)	−0.51	(−5.93, 4.92)	−2.86	(−9.19, 3.47)
	ΣDEHP	−2.18	(−6.95, 2.58)	1.06	(−3.61, 5.73)	0.41	(−4.18, 5.00)
	ΣDBP	−2.99	(−7.57, 1.59)	**−5.53** *	**(−10.2, −0.84)**	**−4.46** *	**(−8.25, −0.67)**

* $p<0.05$.