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EFFECTS OF MATERNAL EXPOSURE TO PHTHALATES AND BISPHENOL A DURING PREGNANCY ON GESTATIONAL AGE

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Abstract

Objective—Phthalates and bisphenol A (BPA) are ubiquitous environmental toxicants, present in high concentrations in numerous consumer products. We hypothesized that maternal exposure to phthalates and BPA in pregnancy is associated with shortened gestation.

Methods—Urinary phthalate and BPA metabolites from 72 pregnant women were measured at the last obstetric clinic visit prior to delivery. Using linear regression models, we estimated the change in gestational age associated with each interquartile range (IQR) increase in phthalate and BPA metabolite concentration.

Results—IQR increases in urinary mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and BPA concentrations were associated with 4.2 and 1.1 day decreases in gestation, respectively. When stratified by gender, these alterations were found only in male infants.

Conclusions—We conclude that MEHHP and BPA (free + glucuronide) are associated with reductions in gestation, with effects observed only in males. Our findings are consistent with the idea that these agents induce gender-specific alterations in signaling via PPAR-γ transcription factor, androgen precursors, and/or inflammatory mediators during the initiation of labor.

Keywords

phthalates; bisphenol A; labor; prematurity; genital; maternal; neonatal

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DECLARATION OF INTEREST

The authors report no declarations of interest.

INTRODUCTION

Environmental exposures to phthalates and bisphenol A (BPA) are ubiquitous. High molecular weight phthalates, such as di(2-ethyl-hexyl) phthalate (DEHP), are used as plasticizers in the manufacture of polyvinyl chloride, which is in perfumes, nail polish, automobile interiors, vinyl shower curtains, wall and floor coverings, food contact applications, and medical devices. In its 3rd National Report on Human Exposure to Environmental Chemicals, the CDC collected urine samples from a randomly selected sample US subjects and detected elevated levels of mono-(2-ethylhexyl) phthalate (MEHP), the primary monoester metabolite of DEHP in humans. They found urine levels of 3.5 μg/l and 13.6 μg/l for the 10^{th} and 90^{th} percentiles, respectively, in this population [1]. Two oxidative DEHP metabolites, mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), indicative of exposure to DEHP, were also present in high concentrations in urine [2]. Lower molecular weight phthalates, such as di-n-butyl phthalate (DBP) and diethyl phthalate (DEP) are used as solvents and plasticizers, present in lacquers, varnishes, perfumes, lotions, cosmetics, and coatings. BPA is used in the manufacture of polycarbonate, epoxy resins, and other plastics in printed circuit boards, composites, and adhesives [3]. Polycarbonates are used for food-contact use, such as in microwave oven-ware, milk and juice containers, baby bottles, and the interior coating of cans, thus posing a substantial risk for exposure to the public. Bisphenol A diglycidyl ether (BADGE), the lowest molecular weight oligomer, is used in commercial liquid epoxy resins. Like phthalates, significant levels of BPA have been found in wastewater, drinking water, air, and dust [4]. Given the continued widespread use of phthalates and BPA in consumer goods and their presence in the environment, it does not seem that avoidance during pregnancy is possible despite increased public awareness of their potential toxicity. With the exception of the Consumer Product Safety Improvement Act of 2008, which regulates only products designed specifically for children, there has been no federal-level restriction of the use of these agents in the United States.

Urinary concentrations of MEHP, MEHHP, and MEOHP, have been shown to be 5–20 times higher in New Jersey mothers prior to elective cesarean deliveries than the U.S. general and female population based on NHANES 2001–2002 data [5]. Phthalate metabolites in maternal urine are also known to be more sensitive biomarkers of exposure than those measured in maternal or cord serum [6]. In our institution, it has previously been shown that hospitalized infants excrete much higher concentrations of MEHP, MEHHP, and MEOHP in their urine than a U.S. population (NHANES) sample [7]. Similarly, BPA has been found in follicular and amniotic fluid, umbilical cord blood, and placental tissue [8–9]. It is present in maternal serum or urine, amniotic fluid, and/or fetal serum at concentrations comparable to those known to interfere with normal development in animals. Mean levels in maternal plasma have been reported from 0.43–3.1 μg/L, with some subjects as high as 22.3 μg/L. Mean amniotic fluid and fetal serum levels are lower (0.5–8.3 and 0.64–2.3 μg/L, respectively) [9–11]. Elevated phthalates in mothers and newborns are concerning because the fetal and neonatal periods represent a particularly vulnerable period of susceptibility to adverse effects of environmental exposures. It is possible that the levels detected affect reproductive and fetal health, constituting an important public health concern. Both

phthalates and BPA can also induce inflammatory activity, potentially shortening gestation by triggering parturition [12–14]. In our investigation, we quantified maternal exposure to phthalate and BPA metabolites in a high-risk obstetrical population at the final prenatal clinic visit before delivery. We hypothesized that elevated levels of phthalates and would be associated with decreased gestational age at delivery.

METHODS

Study population

Seventy two pregnant women were recruited from the High-Risk Obstetric Clinic at Robert Wood Johnson University Hospital. This high risk population was chosen because of the expected higher incidence of prematurity than in a standard obstetric clinic. Subjects were over the age of 18 and expecting singleton infants. All subjects provided informed consent prior to participation in the study, which was approved by the Institutional Review Board (IRB) at the University of Medicine of New Jersey-Robert Wood Johnson Medical School. A detailed medical history, information on household product use, occupation, hobbies, diet, demographic variables, and ethnicity was then collected at this initial visit. At each subsequent clinic visit, we collected a clean-catch urine sample in a phthalate-free container.

Urinary phthalate and BPA metabolite concentrations

Urine samples were stored at −70°C until analyzed. Samples were analyzed using high-performance liquid chromatography–atmospheric pressure chemical ionization tandem mass spectrometry (LC/MS/MS) to quantify: MEHP, monomethyl phthalate (MMP), monoethyl phthalate (MEP), monobutyl phthalate (MBP), monocyclohexyl phthalate (MCHP), MEHHP, mono-3-methyl-7-methyloctyl phthalate (isodecyl, MDP), MEOHP, mono-n-octyl phthalate (MOP), mono-3-methyl-5-dimethylhexyl phthalate (iso-nonyl, MNP), BPA total, BPA sulfate, and BPA glucuronide. The detection limits ranged from 0.1–0.5 ng/ml, with recovery efficiency of 100 ± 12%. All LC/MS measurements were made using a Thermo Fischer LTQ ion trap mass spectrometer. Initially the recovery of all analytes from the urine matrix was measured against aqueous standards. Recoveries ranged from 75% to 123%. The ion chromatograms created with this MS/MS method had almost no background with method detection limits that ranged from 0.05 (mEHP) to 1.0 ng/ml (mEEHP). Analysis of samples was performed using a urine matrix for the calibration standards. Blanks duplicates and separate urine spiked samples were all used as quality controls. Duplicate samples (participant samples split before preparation) agreed to within 14% RD or better with an average relative deviation of 5.9%. Recoveries of external spikes ranged from 94 to 107%.

BPA and its glucuronide and sulfate metabolites were isolated by liquid/liquid extraction using MTBE/hexane, and quantified by LC/MS/MS using an electrospray interface operated in the negative ionization mode. Urine was substituted as the matrix for calibration standards. Recoveries using this method were within 100±10% and duplicate samples agreed within an average of 8.5%. Calibration curves with commercial standards were used to quantify BPA and the glucoronide. In the absence of a commercially available standard for BPA sulfate, concentrations were approximated from glucuronide calibration curves using a modification of a method by Coughlin et al. [15], resulting in internally consistent

values that may overestimate absolute concentrations. All values were normalized to urine specific gravity to account for differences in hydration.

Determination of gestational age

Male and female infants were examined in the nursery at < 72 hrs of age. Birth weight, gestational age, diagnoses, and medications were obtained from the medical chart. Gestational ages were determined based on the best obstetric estimate in the medical record, using either sonographic dating or date of implantation. These were all found to be consistent with physical examination of the infant.

Statistical analysis

Descriptive statistics were calculated for gestational age, as well as for each urinary phthalate metabolite, BPA (free + glucuronide), and BPA sulfate concentration. Separate linear regression models were used to estimate the change in gestational age associated with each interquartile range (IQR) increase in the metabolite concentration. Unadjusted linear regression models were first fit with each of the metabolites, as well as parity, race, and other predictors of gestational age including maternal education, maternal race, gravidity, maternal employment, paternal employment, fast food consumption, maternal age, birth country (US vs. outside of US). Models of individual metabolites were then adjusted by adding parity and maternal race, those variables that were significant in univariate models (here defined as $p<0.15$). From these models, we estimated the change in gestational age associated with each interquartile range increased in phthalate or BPA metabolite concentrations. The same models were rerun after stratifying by gender (n= 40 for boys, 32 for girls). All statistical analyses were done using SAS V.9.2 (© SAS Institute, Inc., Cary, NC).

RESULTS

The characteristics of the 72 pregnant woman enrolled in the study are shown in Table 1. Indications for enrollment in the High-Risk Obstetric Clinic included previous preterm birth (36%), febrile illness (18%), hypertension (19%), diabetes (14%), urinary tract infection (10%), and preterm labor (6%). Forty infants were male (56%), and 32 female (44%). Of these 72 infants, 7 were preterm (32–33 weeks gestation), 14 late preterm (34–36 weeks), and 51 term (37–42 weeks). Table 2 summarizes newborn measurements and gestational age at birth. Gestational age was 37.47 +/− 2.41 weeks (mean +/− SD), with birth weights 3073.35 g +/− 754.91 g.

The DEHP metabolites MEHP, MEHHP, and MEOHP, as well as MEP, MCHP and MBP were all present in maternal urine in measurable quantities, as were BPA and BPA sulfate. MMP, MOP, MNP, and MDP were present at either low concentrations or were below the level of detection and were not analyzed further. MEOHP was highly correlated with mEHP (r=0.80) and MEHHP (r= 0.76), while MEHHP was less well correlated with MEHP (r= 0.50). Lower correlations were also noted for MBP with MCHP and MEHP (r=0.46 and 0.31 respectively), for BPA with MEHHP and MEOHP (r=0.34 and 0.32 respectively), and for BPA with BPA sulfate (r= 0.30).

After adjusting for parity and maternal race, each interquartile range increase in urinary MEHHP concentration was associated with a significant 4.2 day decrease in gestation (95% confidence interval = −7.9, −0.4; Table 3). Similarly, each interquartile range increase in total BPA was associated with a significant 1.1 day decrease in gestation (95% CI = −2.0, −0.1). Although not statistically significant, we observed decreased gestation associated with each interquartile range increase in MEOHP (−0.6 days), MCHP (−0.9 days), MBP (−2.1 days) and BPA sulfate (−0.5 days), but not with MEP or MEHP. Next, we stratified by gender and found that larger and more consistent reductions in gestation were associated with phthalate metabolites in male infants compared to female infants. Gestational effects for BPA (free + glucuronide) were nearly identical in both genders although statistically significant only for the males. We observed significant reductions in gestation associated with interquartile increases in MEHHP (−5.1 days, 95% CI = −9.6, −0.6) and BPA (free + glucuronide) concentrations (−1.1 days, 95% CI = −2.1, −0.1), and non-significant reductions in all other phthalates and metabolites. Conversely, for female infants, we observed generally smaller and non-significant decreases in gestation associated with MEHHP (−1.4 days, 95% CI = −8.4, 5.7), MCHP (−0.4 days, 95% CI = −7.4, 6.7), MBP (−0.5, 95% CI = −6.2, 5.1), and BPA (free + glucuronide) (−1.6, 95% CI = −4.1, 1.0), but no such decreases in gestation were associated with MECP, MEOHP, MEHP, or BPA sulfate.

DISCUSSION

We found that each interquartile increase in maternal urinary mEHHP concentration was associated with a 4.2 day shorter gestation. This effect was observed primarily in males (−5.1 days) but not in female infants. Shortened gestation is consistent with previous animal studies demonstrating spontaneous abortion and preterm delivery in animals exposed to phthalates. In humans, one recent study suggested that MEHP-positive newborns had lower mean gestational age than controls [16]. In an inner-city population, gestational age was shorter by 1.1 days (95% CI: 0.2–1.8 days) for each 1-logarithmic unit increase in specific gravity-adjusted mEHP concentrations, and averaged 5.0 days (95% CI: 2.1–8.0 days) less among subjects with the highest versus lowest quartile concentrations. Results were similar and statistically significant for the other DEHP metabolites [13]. MEHHP is of particular interest because it is one of the most abundant of DEHP metabolites. In one recent cohort, it was found in measurable quantities in the urine of 100% of women and was associated with exposure to body lotions and bottled water [17]. While a deficit of 4.2 days of gestation is not likely to have consequences in healthy full-term pregnancies, it can potentially be clinically relevant for infants delivering near-term.

In contrast to our findings, some investigators have previously reported small increases in gestation associated with increased DEHP metabolites in maternal second or third trimester urine samples. In these studies, 1-logarithmic increases in urinary MEHP and/or oxidative phthalate metabolite concentrations were associated with approximately 1.1 additional days of gestation [18–19]. Another recent study from Japan reported no effect of phthalate metabolites on birth outcomes [20]. It is possible that differences in exposure levels and/or race, ethnicity or other characteristics of the study populations account for these discrepant findings. Alternatively, our population of high-risk mothers may have been particularly susceptible to the biologic actions of phthalates.

Plausible mechanisms for the induction of shorter gestation by phthalates include the induction of inflammation, which can trigger parturition. Several phthalate metabolites, that are present in a high proportion of urine samples from the general U.S. population, are associated with increased serum C-reactive protein and γ-glutamyltransferase, which are markers of inflammation and oxidative stress, respectively [21]. Both DEHP and MEHP bind the transcription factor PPAR-γ, potentially blocking important anti-inflammatory pathways and resulting in inflammatory signaling.

We also found that BPA (free + glucuronide) was associated with shortened gestational period (by 1.1 days/180.1 ng/mL) and that this effect was stronger in males. This is consistent with several recent studies showing that BPA and its metabolite BADGE exert pro-inflammatory effects. Low serum levels (mean ± SD = 2.59 + 5.23 μg/L) have been associated with recurrent miscarriage [22]. Recently, studies in Mexico and China have suggested dose-related effects on the risk of delivery at less than 37 weeks of gestation [12] and low birth weight [23]. BADGE is a competitive inhibitor of PPAR-γ signaling, potentially blocking the protective effects of endogenous and exogenous PPAR-γ agonists. Prenatal exposure of animals to BPA results in decreased immune tolerance to protein allergens [24], as well as reduced numbers of regulatory T cells in mice, promoting increased Th1 responses [25].

The increased susceptibility of males to the induction of prematurity by phthalates is consistent with epidemiologic data suggesting that males are more likely to deliver prematurely, in general [26]. In one study, there was a 7.2% excess of males among white singleton preterm births, distributed uniformly from 20–37 weeks of gestation [27]. Several plausible biologic mechanisms have been proposed for the higher incidence of preterm labor for male infants. These include the action of androgen precursors, which are involved in the production of estrogen and are elevated in male relative to female fetuses [28]. Alternatively, induction of labor may be promoted by interleukin (IL)-1 in males, who have lower levels of IL-1 receptor antagonist in amniotic fluid than females [29].

Our study has several limitations, most notable being the small sample size. We were limited to one urine sample per mother, and thus were unable to assess the variability of each metabolite across the pregnancy. It is not known at what point(s) in gestation infants are most vulnerable to these compounds. Urine samples were obtained at earlier time points in pregnancy in this cohort, and ongoing analyses in further studies may be helpful in addressing this question. The analytic technique was not sensitive enough to measure several of these phthalate metabolites at the very low levels found in urine for a few metabolites (i.e. MMP, MOP, MNP, and MDP). Finally, our study focused on high-risk pregnancies. Thus, our mean gestational age and birth weight was 37.5 weeks and 3073 grams respectively, as compared to statewide means of 38.5 weeks and 3255 grams. A high-risk obstetric population was chosen in order to increase the incidence of shortened gestation in the study group, making the effects of phthalates and BPA more detectible. The main pregnancy diagnoses resulting in identification as high risk (previous preterm birth, hypertension, diabetes, urine infection, and other febrile illnesses—Table 1) are independent of any known effects of phthalates or BPA. Therefore, the “high-risk” women are thought to represent a population with increased susceptibility to effects that may be generalizable to all mothers

and infants. Our findings suggest that MEHHP and BPA (free + glucuronide) are associated with small reductions in gestation, but that these effects are significant only for male infants.

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Table 1

Maternal and neonatal demographics (n=72)

Variable Name	N	%
Maternal		
Age		
18–23	8	11
24–29	18	25
30–35	18	25
36–41	23	32
>41	5	7
Race		
White	23	32
Black	21	29
Hispanic	21	29
Other	7	10
Indications for High Risk		
Congenital Anomalies	4	6
Previous preterm birth	26	36
Preterm labor for current pregnancy	4	6
Diabetes (long standing)	3	4
Diabetes (pregnancy-related/gestational)	7	10
Hypertension (essential)	6	8
Hypertension (pregnancy-related)	8	11
Urinary infection	7	10
Febrile illness	13	18
Other	22	31
Number of Previous Pregnancies		
0	11	15
1	19	26
2	13	18
3	11	15
4	6	8
More	12	17
Number of Previous Live Births		
0	22	31
1	31	43
2	12	17
3	3	4
4	1	1
More	3	4
Neonatal		
Gender		

Variable Name	N	%
Female	32	44
Male	40	56
Gestational age		
Severe preterm (<32 weeks)	0	0
Moderate preterm (32–33 weeks)	7	10
Mild preterm (34–36 weeks)	14	19
Term (37–42 weeks)	51	71
Suspected infection		
Yes	18	25
No	54	75
Respiratory Distress		
Yes	15	21
No	57	79

Table 2

Distribution of newborn measurements and gestational age at birth (n=72)

Measure	# Missing	Mean ± Standard Deviation	Min.	5 TH %tile	25TH %tile	50TH %tile	75TH %tile	95TH %tile	Max.
Birth weight (g)	0	3073.35 ± 754.91	1090.00	1730.0	2462.50	3195.00	3697.50	4180.00	4706.00
Head Circumference (cm)	1	32.97 ± 2.47	23.00	29.00	31.75	33.00	34.93	36.50	39.37
Birth Length (cm)	0	48.26 ± 4.99	19.50	41.50	46.75	49.20	50.80	54.61	55.88
Gestational age (week)	0	37.5 ± 2.4	32	33	36	38	39	41	41

Table 3

Change in gestational age associated with each interquartile range increase in phthalate and BPA metabolite, adjusted for parity and maternal race.

		ALL INFANTS (n=72)			MALES (n=40)			FEMALES (n=32)		
Metabolite	**Inter-quartile range (ng/mL)**	**Change (days)**	**95% confidence interval**	**p-value**	**Change (days)**	**95% confidence interval**	**p-value**	**Change (days)**	**95% confidence interval**	**p-value**
MEP	309.5	0.2	−0.6, 1.0	0.58	−0.02	−1.2, 1.2	0.97	0.3	−0.8, 1.4	0.56
MEHHP	21.9	−4.2	−7.9, −0.4	0.03	−5.1	−9.6, −0.6	0.03	−1.4	−8.4, 5.6	0.69
MEOHP	17.4	−0.6	−2.7, 1.5	0.58	−3.0	−6.4, 0.4	0.08	0.4	−2.4, 3.3	0.76
MCHP	18.6	−0.9	−5.7, 3.9	0.71	−1.7	−9.7, 6.4	0.67	−0.4	−7.4, 6.7	0.92
MEHP	5.8	0.4	−1.1, 2.0	0.59	−0.1	−4.3, 4.0	0.95	0.5	−1.4, 2.3	0.61
MBP	77.8	−2.1	−5.2, 1.1	0.19	−2.8	−6.8, 1.2	0.16	−0.5	−6.2, 5.1	0.85
BPA sulfate	308.9	−0.5	−1.5, 0.4	0.29	−0.7	−1.7, 0.3	0.16	0.1	−2.2, 2.4	0.91
BPA free + glucuronide	180.1	−1.1	−2.0, −0.1	0.03	−1.1	−2.1, −0.1	0.03	−1.6	−4.1, 1.0	0.21