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Preterm birth in relation to the bisphenol A replacement, bisphenol S, and other phenols and parabens

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Abstract

Introduction: Preterm birth continues to be a significant public health concern and is a leading cause of perinatal and infant mortality. Environmental exposures to phenols and parabens are suspected to potentially contribute to the pathology of preterm birth, yet limited human studies have characterized the extent to which these toxicants are associated with birth outcomes.

Methods: We examined the associations between phenols, parabens, and preterm birth, within pregnant women who were recruited early in gestation into the LIFECODES cohort at Brigham and Women's Hospital in Boston, Massachusetts. Urine samples were collected at up to 4 time points in pregnancy and analyzed for phenols and parabens. We selected 130 cases of preterm birth (defined as delivery before 37 weeks gestation), and 350 random controls. We categorized preterm birth subtypes based on clinical presentation and identified 75 cases of spontaneous preterm birth (characterized by spontaneous preterm labor and/or preterm premature rupture of membranes), and 37 cases of placental preterm birth (characterized by preeclampsia and/or intrauterine growth restriction). We used multivariate logistic regression with visit specific and geometric averages of phenols and parabens to determine associations with preterm birth.

Results: We observed moderate variability in urinary phenol and paraben concentrations over pregnancy with intraclass correlation coefficients ranging between 0.45 – 0.68. Regression analyses indicated mostly null associations. We observed inverse associations, notably between 2,5-dichlorophenol and overall preterm birth (adjusted odds ratio [95% confidence interval, CI]: 0.79 [0.67 – 0.94]), and this relationship was consistent by study visit. Conversely, ethyl paraben was associated with increased risk for placental preterm birth (adjusted odds ratio [95% CI]: 1.47

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[1.14 – 1.91]). Bisphenol-S detection at visit 4 was associated with overall preterm birth (adjusted odds ratio [95% CI]: 2.05 [1.09, 3.89]).

Conclusions: While the findings from this study largely indicate null associations, we observed some relationships between select phenols, parabens and preterm birth, which warrants further investigation of these toxicants and birth outcomes.

Keywords

Preterm birth and subtypes; phenols; parabens; repeated measures

1. INTRODUCTION

Preterm birth (defined as delivery at less than 37 weeks gestation) is the leading cause of perinatal and infant mortality in the U.S (Callaghan et al. 2006; Klebanoff and Keim 2011), and the second leading cause of death in children under the age of 5 worldwide (Blencowe et al. 2012). Additionally, preterm birth is associated with serious short- and long-term complications, including blindness, deafness, cerebral palsy, developmental disorders (physical, psychological, behavioral, emotional), and chronic health problems such as poor respiratory function, cardiovascular disease, and insulin resistance (Institute of Medicine 2007; Moster et al. 2008). Despite a slight decrease in rates over the past several years, the rate of preterm births has increased significantly in the U.S. since 1981, and currently comprise approximately 10% of all live births (Martin et al. 2017). There are extremely high medical and societal costs associated with the large number of babies being born prematurely (Institute of Medicine 2007). The causes of the majority of preterm births remain unexplained, and interventions geared toward known causes are projected to result in a modest reduction in preterm births (Chang et al. 2013; Schoen et al. 2015). The role of environmental pollutants as potential contributing factors to preterm birth has been greatly understudied (Institute of Medicine 2007). Establishing links between environmental exposures and preterm birth may represent an opportunity for large public health impact since many exposures may be modifiable through intervention strategies.

Phenols broadly comprise chemical compounds with hydroxyl groups bonded to an aromatic hydrocarbon, and parabens are a subset of phenols that contain an ester group on the aromatic hydrocarbon in addition to the hydroxyl group. Various phenols and parabens are used in personal care and other consumer products, resulting in widespread human exposure (Centers for Disease Control and Prevention 2017b). Bisphenol-A (BPA), the most-studied of phenolic compounds is used in polycarbonate plastics, epoxy resins, and thermal paper with numerous downstream applications (Vandenberg et al. 2007). Due to growing demand for BPA-free products stemming from toxicity and health concerns, the use of and human exposure to replacement chemicals for these applications, such as bisphenol-S (BPS), may be increasing rapidly (Ye et al. 2015). This is of concern since the potential health consequences following exposure to BPS have been much less studied than BPA, although it could possess similar toxicity (Rochester and Bolden 2015). Among other common environmental phenols for which pervasive exposure has been demonstrated, benzophenone-3 (BP3) is a UV filter found in many sunscreens, face lotions, and other products such as cosmetics, conditioners, and plastics (Calafat et al. 2008). The chemicals

2,4-dichlorophenol (2,4-DCP) and 2,5-dichlorophenol (2,5-DCP) are measurable in a high proportion of human urine samples due to common use in pesticides and deodorizers (Meeker et al. 2013; Ye et al. 2014). Triclosan (TCS) and triclocarban (TCB) are antimicrobial agents most commonly used in soaps, toothpastes, mouthwash, lotions, deodorants, and various medical products (Calafat et al. 2007; Meeker et al. 2013). Finally, parabens are also antimicrobials that are used as preservatives in many cosmetics, as well as in some packaged foods and pharmaceuticals (Calafat et al. 2010; Meeker et al. 2013).

A growing number of studies have assessed relationships between exposure to BPA and birth outcomes, including fetal growth, gestational age, preterm birth, and birth weight (Cantonwine et al. 2010; Chou et al. 2011; Feng et al. 2016; Ferguson et al. 2017; Huo et al. 2015; Lee et al. 2014; Miao et al. 2011; Snijder et al. 2013; Troisi et al. 2014). Limited studies of chlorinated phenols (TCB, TCS, dichlorophenols) and parabens have reported suggestive evidence for various associations with birth weight, length, and/or head circumference (Geer et al. 2017; Guo et al. 2016a; Philippat et al. 2012; Tang et al. 2013a; Wolff et al. 2008). There has been one previous study investigating the BPA analogue BPS during pregnancy (Wan et al. 2018), however, our study is the first to evaluate repeated measurements of BPS.

We previously reported suggestive associations between bisphenol A (BPA) and preterm birth (Cantonwine et al. 2015). Since the time of that publication, separate aliquots of the same samples from the study participants were re-analyzed to measure a larger panel of environmental phenols and parabens. The present study aimed to investigate the risk of preterm birth in association with urinary concentrations of phenols (2,4-DCP, 2,5-DCP, BP3, BPS, TCB, and TCS) and parabens (methyl, ethyl, propyl, and butyl parabens), using biomarkers of exposure measured at up to 4 time points in pregnancy.

2. METHODS

2.1 Study Population

The LIFECODES birth cohort is an ongoing prospective birth cohort conducted at Brigham and Women's Hospital in Boston, Massachusetts, USA. Between October 2006 and September 2008, 1,648 women ages 18–50 delivered as part of the cohort. Pregnant women who planned to deliver at Brigham and Women's Hospital were recruited to participate in their first trimester. Exclusion criteria included higher-order multiple gestations (triplets or greater). Written informed consent was obtained from participants, and study protocols were approved by the institutional review boards of the Brigham and Women's Hospital and the University of Michigan. Upon enrollment into the study, at the first study visit (median 9.7 [Interquartile Range (IQR): 3.28] weeks gestation), participants completed demographic questionnaires to provide information on race/ethnicity, tobacco and alcohol use, and other factors, in addition to providing urine and blood samples for biomarker analysis. During the three subsequent visits (median 17.9 [IQR: 1.71] weeks, 26.0 [IQR: 1.89] weeks, and 35.0 [IQR: 1.28] weeks), additional biological samples were collected as well as clinically relevant pregnancy characteristics. All gestational age dating was validated by first trimester ultrasound measurements.

To investigate the relationship of environmental exposures with preterm birth, we designed a nested case control study including 130 singleton preterm birth cases and 350 randomly selected singleton controls who delivered at or after 37 weeks. Among preterm births, we further classified cases by clinical presentation (McElrath et al. 2008). 75 cases were classified as “spontaneous” preterm birth, characterized by clinical presentation of spontaneous preterm labor and/or preterm premature rupture of membranes (PPROM); 37 were classified as “placental” preterm birth, characterized by preeclampsia or intrauterine growth restriction (Cantonwine et al. 2015). An additional 18 cases were not included in this subset analysis since medical protocol required their delivery prior to 37 weeks. These cases included the management of prior classical cesarean section, abdominal cerclage, prior term intrauterine demise, and suspected uterine thinning due to prior surgery. These types of cases have no suspected unifying etiology and were thus not analyzed separately.

2.2 Urinary Exposure Biomarkers

Urine was collected in polypropylene containers, divided into aliquots, and stored at -80°C until shipped to the laboratory at NSF International (Ann Arbor, MI) where they were analyzed for total BPS, BP3, TCS, TCB, 2,4-DCP, 2,5-DCP, butyl paraben, ethyl paraben, methyl paraben, and propyl paraben. The analytical method was based on the Centers for Disease Control and Prevention (CDC) method used in U.S. National Health and Nutrition Examination Survey (NHANES) investigations (Ferguson et al. 2017). Briefly, samples underwent enzymatic deconjugation, solid phase extraction, and analysis with a triple quadrupole mass spectrometer.

For analytes detected in at least 60% of samples, levels below the limit of detection (LOD) were replaced by dividing the LOD by the square root of two (Hornung and Reed 1990). Specific gravity was measured in the urine samples to account for urinary dilution within the study population. For univariate and bivariate statistics, we corrected all urinary biomarkers using specific gravity as follows:

$$UB_{SG} = UB \times \frac{SG_{Median} - 1}{SG - 1}$$

UB_{SG} is the specific gravity-corrected urinary biomarker concentration (ng/mL), UB is the measured and uncorrected urinary biomarker concentration, SG_{Median} (1.015) is a constant for the population median specific gravity, and SG is the observed specific gravity of a given urine sample (Meeker et al. 2009).

2.3 Statistical Analysis

Analysis was performed using R version 3.4.0. We characterized the proportion of preterm birth cases and controls in relation to several covariates, which included maternal age, maternal race/ethnicity, pre-pregnancy BMI, health insurance, maternal education level, fetal sex, history of assisted reproductive therapy (ART), history of in vitro fertilization (IVF), parity, gravidity, and maternal smoking and alcohol use during pregnancy. Although we did not have measures of participant household income, health insurance provider (Private/HMO/Self-pay vs. Medicaid/SSI/MassHealth) is an indirect indicator of income

status. Pairwise Spearman correlation coefficients were calculated for individual specific gravity-corrected urinary analytes. Bivariate associations were then determined between specific gravity-corrected urinary analytes in relation to the aforementioned covariates to determine variable eligibility for building regression models in a forward stepwise manner. We then examined temporal variability in specific gravity-corrected urinary phenol and paraben concentrations by subject for analytes with at least 60% detection, through estimation of intraclass correlation coefficients (ICC). To estimate the ICC's, we used the *ICCest* function from the ICC package (v2.3.0) in R, which estimates ICC and confidence intervals using variance components from a one-way analysis of variance using the THD option (Thomas and Hultquist 1978). These parameters represent the ratio of intra-individual variability to the sum of intra and inter-individual variability and range from zero to one, where values equal to one indicate no intra-individual variability (Rosner 2011).

Associations between phenols, parabens, and preterm birth were estimated using multivariate logistic regression. We calculated subject-specific geometric averages of phenols and parabens (unadjusted for specific-gravity) measured in urine samples collected at visits 1–3 (hereafter referred to as average exposure). Average exposures were used as a more stable estimate of maternal exposure across the course of gestation. Although this data can be analyzed using hierarchical logistic regression, we have previously tested both approaches and found that either approach is appropriate for the present data and produce comparable results (Chen et al. 2015). To account for urinary dilution, we modeled average specific gravity as a covariate in adjusted models, a method that several previous environmental epidemiology studies have recommended (Adibi et al. 2009; Buser et al. 2014; Tang et al. 2013b; Wolff et al. 2008; 2017). TCB and BPS had low detection rates (6.0 and 20% respectively), and we modeled these analytes as categorical predictors (i.e., detected in any of the repeated samples vs. all samples with non-detection). Measurements from visit 4 were excluded from analysis of average exposure as they were less commonly measured in cases of preterm birth compared to controls.

To assess windows of vulnerability to exposure during pregnancy, we conducted stratified logistic regression, based on study visit. In these analyses, we estimated associations with overall preterm birth and subtypes by conducting logistic regression for each study visit. Covariates that were significantly associated with exposures were examined for inclusion in adjusted logistic regression models. Inclusion of covariates for fully adjusted models was determined using a forward stepwise approach, in which variables were selected if they changed the beta coefficient of the phenol analyte by 10% or more. Models were built using average exposure measurements. The final multivariable logistic regression models were adjusted for maternal age, specific gravity (average or visit-specific), race/ethnicity (White, African-American, or other), pre-pregnancy body mass index (BMI), health insurance provider (Private/HMO/Self-pay vs. Medicaid/SSI/MassHealth), and education level (High school, technical school, some college, or college graduate). All models were adjusted for the same sets of covariates for comparability across phenols.

In secondary analyses, we examined associations between phenols, parabens, and preterm birth subtypes. For models of spontaneous preterm birth, cases with other preterm presentations were excluded. Likewise, for models of placental preterm birth, cases with

other preterm presentations were excluded. Second, because of the potential for sex differences in the relationships between phenols, parabens, and reproductive outcomes that have been demonstrated in studies of fetal growth (Casas et al. 2016; Ferguson et al. 2017; Guo et al. 2016b; Lassen et al. 2016; Tang et al. 2013b; Wu et al. 2017), we conducted analyses stratified by infant sex and calculated sex-specific interaction terms using the method described by Buckley et al. (Buckley et al. 2017). Due to the use of BPA in the same products as BPS, we accounted for potential confounding by including urinary BPA concentrations in BPS models. In previous studies, we reported associations between the following phthalate metabolites and preterm birth: Mono-(2-ethyl)-hexyl phthalate (MEHP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-n-butyl phthalate (MBP), and mono-(3-carboxypropyl) phthalate (MCP) (Ferguson et al. 2014a; 2014b). To evaluate the robustness of our findings and account for potential confounding due to coexposure with these phthalate metabolites, we conducted an additional sensitivity analysis where we further adjusted for MEHP, MECP, MBP, and MCP, individually in each model of phenols and parabens. We further evaluated the robustness of our findings by modeling for multiple phenols and parabens in the same adjusted logistic regression model, including only select toxicants that were associated in single pollutant adjusted logistic regression models.

3. RESULTS

The primary demographic information on this study population are reported in Table 1. Briefly, the median maternal age was 32.7 years, and just over half of participants had a normal pre-pregnancy BMI (52% had BMI <25, 26% had BMI 25 but <30, and 21% had BMI ≥30) (Table 1). Participants were primarily white (59%), college graduates (39%), and did not use tobacco (92%) or alcohol (94%) during pregnancy (Table 1). There were no statistically significant differences in demographic variables between preterm birth cases and controls (Table 1).

There were 1,651 urine samples collected from the 480 women available for analysis. Most of the analytes were detected in a high proportion of samples (Table 2). BP3 and methyl paraben were detected in the most samples (>99%), while BPS (20%) and TCB (6%) were detected the least (Table 2). Concentrations of urinary phenols and parabens that we measured were mostly comparable to concentrations in pregnant women from the NHANES (2005 – 2010) and the National Children's Study (2009 – 2010) (Mortensen et al. 2014). However, we did observe higher median concentrations for methyl paraben (LIFECODES: 151 ng/mL; NHANES: 84.7 ng/mL; NCS: 105 ng/mL) and propyl paraben (LIFECODES: 37 ng/mL; NHANES: 20.6 ng/mL; NCS: 22.3 ng/mL) (Centers for Disease Control and Prevention 2017b; Mortensen et al. 2014).

The biomarkers detected in 60% of urine samples showed overall moderate temporal reliability in the ICC analysis (Table 3). 2,5-DCP had the highest ICC (0.7), followed by BP3 (0.55) (Table 3). Triclosan and the parabens all had ICC near 0.5 (Table 3). Correcting biomarker concentrations by specific gravity had minimal impact on the ICC values (Table 3).

In relation to demographic variables, BP3 concentrations were higher with maternal age whereas methyl paraben, propyl paraben, 2,4-DCP, and 2,5-DCP were lower with increasing age (Supplemental Table 2). Education followed similar trends to maternal age for these same exposure biomarkers. We observed higher concentrations of dichlorophenols among participants with higher BMI, and lower concentrations of BP3, butyl paraben, and ethyl paraben among participants with higher BMI (Supplemental Table 2). White mothers had lower concentrations of most of the analytes compared to other races (Supplemental Table 2). Finally, women with public health insurance had higher concentrations of parabens and dichlorophenols, but lower concentrations of BP3, compared to women with private insurance (Supplemental Table 2).

Results from crude models were generally similar to those from adjusted multivariable models throughout (Table 4 and Supplemental Table 3). For analytes detected in 60% of samples, average urinary concentrations of 2,5-DCP was associated with decreased odds of overall, spontaneous, and placental preterm birth (Table 4). We also observed increased odds of placental preterm birth in relation to ethyl paraben (adjusted odds ratio (aOR) [95% confidence interval, CI]=1.47 [1.14 – 1.91]) (Table 4). When exploring associations between exposure biomarker concentration at each visit, the reduced odds for preterm birth in association with 2,5-DCP were generally consistent throughout pregnancy, though the relative magnitude of the relationship between spontaneous and placental preterm birth varied (Figure 1 and Supplemental Table 4). Stratified analyses also indicated that TCS was associated with decreased odds of spontaneous preterm birth at visit 2 (aOR [95% CI]=0.81 [0.68, 0.96]) (Supplemental Table 4). We observed a positive association between ethyl paraben and placental preterm birth at visit 2 (aOR [95% CI]=1.35 [1.06 – 1.71]) (Supplemental Table 4).

In order to characterize relationships with covariates, in Supplemental Table 5 we reported odds ratios for each of the covariates from the adjusted models of the exposures that were associated with outcome variables (2,5-DCP, ethyl paraben, and TCS). We observed that women who were college graduates had lower odds of overall preterm birth, and the greatest effect was observed in the model with 2,5-DCP (aOR [95% CI] = 0.38 [0.16 – 0.91]) (Supplemental Table 5). We also observed that pre-pregnancy BMI was associated with a small increase in odds for placental preterm birth, and the greatest effect was observed in the model with ethyl paraben (aOR [95% CI] = 1.12 [1.05 – 1.20]) (Supplemental Table 5).

For the biomarkers detected in less than 60% of samples (BPS and TCB), we modeled the odds of preterm birth in relation to detection of the chemicals (Figure 1 and Supplemental Tables 6 and 7). No associations were observed when combining exposure data from the multiple visits (i.e., detected BPS or TCB in any of the repeated samples vs. all non-detect). However, when exploring associations by visit, BPS detection at visit 4 was associated with increased odds of overall preterm birth (aOR [95% CI]=2.05 [1.09 – 3.89]; Figure 1 and Supplemental Table 7). When further exploring preterm birth subtypes, detection of BPS at visit 4 was suggestively associated with increased odds for both spontaneous preterm birth (aOR [95% CI]=2.23 [0.98 – 12.2]) and placental preterm birth (aOR [95% CI]=3.45 [0.98 – 12.2]) (Supplemental Table 7). Sensitivity analysis with additional adjustment of BPA in models with BPS revealed similar relationships, where detection of BPS remained

associated with an aOR of 1.92 (95% CI: 1.01 – 3.68) (Supplemental Table 9). In the sensitivity analysis with stratification by fetal sex, we did not observe any differences in associations by fetal sex (p -interaction > 0.05). The results from our sensitivity analysis of adjusting for select phthalate metabolites indicated that associations from single pollutant models did not change appreciably, where effect estimates and p -values were within 10% change (Table 4 and Supplemental Table 9). In our sensitivity analysis of multi-pollutant adjusted models, we included 2,5-DCP, ethyl paraben, and TCS, since each of these were associated with preterm birth in the single pollutant models. These results indicated that effect estimates and p -values were also within 10% change of results from single pollutant models (Table 4).

4. DISCUSSION

In this case-control study of preterm birth among women in the LIFECODES prospective birth cohort, we observed mostly null associations. Ethyl paraben associated with elevated risk for preterm birth, whereas 2,5-DCP and TCS were associated with reduced risk. These associations differed by preterm birth subtypes and by visit of sample collection.

To our knowledge this is the largest study of preterm birth in relation to exposure to this class of chemicals. One recent study of 185 pregnant women in Brooklyn, NY assessed the relationship between urinary TCS, TCB, and parabens in relation to preterm birth (Geer et al. 2017). They reported that none of the urinary biomarkers were significantly associated with odds of preterm birth, however, the study included a small number of overall preterm birth cases ($n=43$). Geer et al. (2017) reported an inverse association between maternal urinary butyl paraben and gestational age at birth, but no associations with maternal urinary TCS, TCB, methyl paraben, or ethyl paraben. A Chinese study of 567 pregnant women that measured urinary BP3 reported an inverse relationship with gestational duration (Tang et al. 2013), however, BP3 concentrations in that study (median 0.08 ng/ml) were orders of magnitude lower than those measured in the present population (median 36.0 ng/ml). Each of these earlier studies collected a single urine sample during pregnancy for exposure assessment, with many of them collected at the time of hospital admission for delivery. Based on our findings of the ICC ranges for phenols, urinary concentrations may not be very stable and thus requires multiple repeated measurements to provide a more accurate exposure assessment. These studies also did not assess associations with preterm birth and its subtypes. Although we tested for associations within preterm birth subtypes, one limitation of this case subsetting is that the sample size for placental ($n=33$) and spontaneous ($n=71$) preterm birth subtypes in adjusted models were much smaller. Due to these smaller sample sizes in preterm birth subtypes, some true associations may not have been detected in our study.

We reported that higher levels of ethyl paraben were associated with an increased odds of placental preterm birth, and this association was largely driven by elevated levels measured at visits 1 and 2 – spanning gestational weeks from both the first and second trimester. Relationships observed from visits 1 and 2 reflect exposures taking place early in pregnancy, and these effects are likely secondary to perturbations in vascularization and placentaion in early gestation (Nijman et al. 2016). Ethyl paraben may interact with estrogen and

progesterone receptors (Bł dzka et al. 2014; Kiyama and Wada-Kiyama 2015a). By interfering with receptor signaling, ethyl paraben has the potential to influence placental development by altering the vascularization necessary for placental development (Kiyama and Wada-Kiyama 2015b; Thompson et al. 2015). Abnormal placental development is associated with cardiometabolic irregularities and complications in pregnancy including preeclampsia and intrauterine growth restriction, leading to the placental subtype of preterm delivery (Reijnders et al. 2017).

At study visit 4, BPS detection in the last trimester of pregnancy was associated with increased odds for overall as well as for both subtypes of preterm birth. BPS is structurally and chemically similar to BPA, and several studies have indicated that it can act through similar mechanistic pathways (Rochester and Bolden 2015). Although BPA was not associated with overall preterm birth in our previous study, we also observed a relationship at study visit 4, where higher concentrations of BPA was associated with an increased risk for spontaneous preterm birth (Cantonwine et al. 2015). The associations we observed with BPS remained consistent with additional adjustment of BPA in statistical models. However, compared to visits 1 – 3 ($n_{\text{cases}} = 92 - 119$), we observed a decline in study participants at visit 4 ($n_{\text{cases}} = 63$) due to some having already delivered preterm. Consequently, the associations that we characterized at visit 4 suffer from potential bias due to loss of cases. In contrast to our findings, Wan et al. (2018) observed high BPS detection in a large sample of pregnant women ($N=985$), and found that higher concentrations of BPS from maternal single spot urine samples was associated with increased pregnancy duration. The detection rate of BPS was very low in our present study, largely because the study took place between 2006 and 2008. Future studies will likely observe higher levels of BPS, given that replacement of products with BPS became more prominent after this period (Liao et al. 2012; Wan et al. 2018).

In contrast to these findings, we found evidence of protective effects of 2,5-DCP and TCS. Decreased odds of spontaneous, placental, and overall preterm birth were associated with higher concentrations of 2,5-DCP. Detection of chlorinated phenols can result from chlorinating water sources for disinfection from environmental pathogens, therefore it is possible that higher concentrations of 2,5-DCP in drinking water are a proxy for chlorination of water sources and highly correlated with decreased microbial pathogens in drinking water (undefined author; ATSDR 1999; Centers for Disease Control and Prevention 2017a). Furthermore, the use of TCS as an antimicrobial in soaps could result in a decrease in microbial exposure for women during pregnancy. Future studies may need to better account for area of residence as a confounder for preterm birth, and test whether or not water treatment is specifically associated with elevated concentrations of 2,5-DCP and TCS in drinking water.

Our study had some limitations that should be highlighted in order to improve future investigations of environmental exposures and reproductive health. First, our study does not contain data on dietary patterns, which may be a confounder for phenol and paraben exposure and preterm birth (Hartle et al. 2016; Karnjanapiboonwong et al. 2011; Mancini et al. 2015; Ramaswamy et al. 2011). Second, we do not have data on direct socioeconomic metrics such as household income, which can be an important predictor of environmental

exposures and preterm birth. Additionally, although we measured urine from several time points, urinary concentrations of phenols are still highly variable; therefore urinary measurements are reflective of recent exposures and can result in non-differential measurement error. This would be particularly problematic for our assessment of windows of vulnerability to exposure. Additionally, birth outcomes are responsive to exposures of other classes of toxicants, such as heavy metals and persistent organic pollutants (Ferguson and Chin 2017; Rahman et al. 2016). The present study does not account for co-exposure to these toxicants; however, future studies should consider evaluating multiple classes of toxicants together in order to elucidate the effect of toxicant mixtures on preterm birth. Last, we conducted several statistical comparisons. As such, some associations may have resulted from chance. Despite this limitation, these associations are suggestive and deserve additional investigation in future studies.

Despite these limitations, our study is characterized by several strengths. First, we collected up to four urine samples from a large sample size of study participants, which resulted in a robust exposure assessment of environmental phenols. The time span of sample collection across gestation also afforded greater understanding of windows of vulnerability. In our study we also used modern, highly sensitive analytical methods to measure urinary analytes. Last, our study leveraged a comprehensive assessment of preterm delivery and subtypes. These outcome variables were determined using gestational dates that were validated clinically and with first-trimester ultrasonography.

5. CONCLUSIONS

In this case control study of pregnant women, we reported mostly null associations between environmental phenols, parabens, and preterm birth. Among the notable associations, ethyl paraben was associated with an increased risk for placental preterm birth. Visit specific associations revealed that BPS detection at visit 4 was also associated with increased risk for preterm birth. Meanwhile, 2,5-DCP was associated with a decreased risk for overall and spontaneous preterm birth. These associations warrant further investigation and verification in larger studies of preterm birth.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BPA	Bisphenol-A
BPS	Bisphenol-S
BP3	Benzophenone-3
2,4-DCP	2,4-Dichlorophenol
2,5-DCP	2,5-Dichlorophenol
TCS	Triclosan
TCB	Triclocarban
IQR	Interquartile range
NHANES	National Health and Nutrition Examination Survey
CDC	Centers for Disease Control and Prevention
LOD	Limit of detection
SG	Specific gravity
ICC	Interclass correlation coefficients
BMI	Body mass index
ART	Assisted reproductive technology
IVF	<i>In-vitro</i> fertilization

References

- Adibi JJ, Hauser R, Williams PL, Whyatt RM, Calafat AM, Nelson H, et al. 2009 Maternal Urinary Metabolites of Di-(2-Ethylhexyl) Phthalate in Relation to the Timing of Labor in a US Multicenter Pregnancy Cohort Study. *American Journal of Epidemiology* 169:1015–1024; doi:10.1093/aje/kwp001. [PubMed: 19251754]
- ATSDR. 1999 Public Health Statement Chlorophenols. 1–6.
- Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, et al. 2012 National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *The Lancet* 379:2162–2172; doi:10.1016/S0140-6736(12)60820-4.
- Buckley JP, Doherty BT, Keil AP, Engel SM. 2017 Statistical Approaches for Estimating Sex-Specific Effects in Endocrine Disruptors Research. *Environ Health Perspect* 125:067013; doi:10.1289/EHP334. [PubMed: 28665274]
- Buser MC, Murray HE, Scinicariello F. 2014 Association of urinary phenols with increased body weight measures and obesity in children and adolescents. *The Journal of Pediatrics* 165:744–749; doi:10.1016/j.jpeds.2014.06.039. [PubMed: 25063718]
- Błaska D, Gromadzińska J, Wsowicz W. 2014 Parabens. From environmental studies to human health. *Environment International* 67:27–42; doi:10.1016/j.envint.2014.02.007. [PubMed: 24657492]

- Calafat AM, Wong L-Y, Ye X, Reidy JA, Needham LL. 2008 Concentrations of the Sunscreen Agent Benzophenone-3 in Residents of the United States: National Health and Nutrition Examination Survey 2003–2004. *Environ Health Perspect* 116:893–897; doi:10.1289/ehp.11269. [PubMed: 18629311]
- Calafat AM, Ye X, Wong L-Y, Bishop AM, Needham LL. 2010 Urinary Concentrations of Four Parabens in the U.S. Population: NHANES 2005–2006. *Environ Health Perspect* 118:679–685; doi: 10.1289/ehp.0901560. [PubMed: 20056562]
- Calafat AM, Ye X, Wong L-Y, Reidy JA, Needham LL. 2007 Urinary Concentrations of Triclosan in the U.S. Population: 2003–2004. *Environ Health Perspect* 116:303–307; doi:10.1289/ehp.10768.
- Callaghan WM, MacDorman MF, Rasmussen SA, Qin C, Lackritz EM. 2006 The contribution of preterm birth to infant mortality rates in the United States. *Pediatrics* 118:1566–1573; doi:10.1542/peds.2006-0860. [PubMed: 17015548]
- Cantonwine D, Meeker JD, Hu H, Sánchez BN, Lamadrid-Figueroa H, Mercado-García A, et al. 2010 Bisphenol A exposure in Mexico City and risk of prematurity: a pilot nested case control study. *Environmental Health* 9:62; doi:10.1186/1476-069X-9-62. [PubMed: 20955576]
- Cantonwine DE, Ferguson KK, Mukherjee B, McElrath TF, Meeker JD. 2015 Urinary Bisphenol A Levels during Pregnancy and Risk of Preterm Birth. *Environ Health Perspect* 1–7; doi:10.1289/ehp.1408126.
- Casas M, Valvi D, Ballesteros-Gomez A, Gascon M, Fernández MF, Garcia-Esteban R, et al. 2016 Exposure to Bisphenol A and Phthalates during Pregnancy and Ultrasound Measures of Fetal Growth in the INMA-Sabadell Cohort. *Environ Health Perspect* 124:1–8; doi:10.1289/ehp.1409190. [PubMed: 26058085]
- Centers for Disease Control and Prevention. 2017a Effectiveness of Chlorination on Inactivating Selected Pathogen. <https://www.cdc.gov/safewater/effectiveness-on-pathogens.html> 1–3. Available: <https://www.cdc.gov/safewater/effectiveness-on-pathogens.html> [accessed 13 December 2017a].
- Centers for Disease Control and Prevention. 2017b Fourth National Report on Human Exposure to Environmental Chemicals Update. 1–1095.
- Chang HH, Larson J, Blencowe H, Spong CY, Howson CP, Cairns-Smith S, et al. 2013 Preventing preterm births: analysis of trends and potential reductions with interventions in 39 countries with very high human development index. *The Lancet* 381:223–234; doi:10.1016/S0140-6736(12)61856-X.
- Chen Y-H, Ferguson KK, Meeker JD, McElrath TF, Mukherjee B. 2015 Statistical methods for modeling repeated measures of maternal environmental exposure biomarkers during pregnancy in association with preterm birth. *Environmental Health* 14:1117–13; doi:10.1186/1476-069X-14-9.
- Chou W-C, Chen J-L, Lin C-F, Chen Y-C, Shih F-C, Chuang C-Y. 2011 Biomonitoring of bisphenol A concentrations in maternal and umbilical cord blood in regard to birth outcomes and adipokine expression: a birth cohort study in Taiwan. *Environmental Health* 10:94; doi: 10.1186/1476-069X-10-94. [PubMed: 22050967]
- Feng Y, Jiao Z, Shi J, Li M, Guo Q, Shao B. 2016 Effects of bisphenol analogues on steroidogenic gene expression and hormone synthesis in H295R cells. *Chemosphere* 147:9–19; doi:10.1016/j.chemosphere.2015.12.081. [PubMed: 26751127]
- Ferguson KK, Chin HB. 2017 Environmental chemicals and preterm birth: Biological mechanisms and the state of the science. *Curr Epidemiol Rep* 4:56–71; doi:10.1007/s40471-017-0099-7. [PubMed: 28944158]
- Ferguson KK, McElrath TF, Ko Y-A, Mukherjee B, Meeker JD. 2014a Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. *Environment International* 70:118–124; doi:10.1016/j.envint.2014.05.016. [PubMed: 24934852]
- Ferguson KK, McElrath TF, Meeker JD. 2014b Environmental Phthalate Exposure and Preterm Birth. *JAMA Pediatr* 168:61–7; doi:10.1001/jamapediatrics.2013.3699. [PubMed: 24247736]
- Ferguson KK, Meeker JD, Cantonwine DE, Mukherjee B, Pace GG, Weller D, et al. 2017 Environmental phenol associations with ultrasound and delivery measures of fetal growth. *Environment International* 112:243–250; doi:10.1016/j.envint.2017.12.011. [PubMed: 29294443]
- Geer LA, Pycke BFG, Waxenbaum J, Sherer DM, Abulafia O, Halden RU. 2017 Association of birth outcomes with fetal exposure to parabens, triclosan and triclocarban in an immigrant population in

- Brooklyn, New York. *Journal of Hazardous Materials* 323:177–183; doi:10.1016/j.jhazmat.2016.03.028. [PubMed: 27156397]
- Guo J, Wu C, Lv S, Lu D, Feng C, Qi X, et al. 2016a Associations of prenatal exposure to five chlorophenols with adverse birth outcomes. *Environmental Pollution* 214:478–484; doi:10.1016/j.envpol.2016.04.074. [PubMed: 27131805]
- Guo J, Wu C, Lv S, Lu D, Feng C, Qi X, et al. 2016b Associations of prenatal exposure to five chlorophenols with adverse birth outcomes. *Environmental Pollution* 214:478–484; doi:10.1016/j.envpol.2016.04.074. [PubMed: 27131805]
- Hartle JC, Navas-Acien A, Lawrence RS. 2016 The consumption of canned food and beverages and urinary Bisphenol A concentrations in NHANES 2003–2008. *Environmental Research* 150:375–382; doi:10.1016/j.envres.2016.06.008. [PubMed: 27362993]
- Hornung RW, Reed LD. 1990 Estimation of Average Concentration in the Presence of Nondetectable Values. *Applied Occupational and Environmental Hygiene* 5:46–51; doi:10.1080/1047322x.1990.10389587.
- HSDB. 2,5-Dichlorophenol. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?/.temp/~x3jKB:3> Available: <https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?/.temp/~x3jKB:3> [accessed 13 December 2017].
- Huo W, Xia W, Wan Y, Bin Zhang, Zhou A, Zhang Y, et al. 2015 Maternal urinary bisphenol A levels and infant low birth weight: A nested case–control study of the Health Baby Cohort in China. *Environment International* 85:96–103; doi:10.1016/j.envint.2015.09.005. [PubMed: 26382648]
- Institute of Medicine. 2007 Preterm Birth: Causes, Consequences, and Prevention. doi: 10.17226/11622.
- Karnjanapiboonwong A, Chase DA, Cañas JE, Jackson WA, Maul JD, Morse AN, et al. 2011 Uptake of 17 α -ethynylestradiol and triclosan in pinto bean, *Phaseolus vulgaris*. *Ecotoxicology and Environmental Safety* 74:1336–1342; doi:10.1016/j.ecoenv.2011.03.013. [PubMed: 21513980]
- Kiyama R, Wada-Kiyama Y. 2015a Estrogenic endocrine disruptors: Molecular mechanisms of action. *Environment International* 83:11–40; doi:10.1016/j.envint.2015.05.012. [PubMed: 26073844]
- Kiyama R, Wada-Kiyama Y. 2015b Estrogenic endocrine disruptors: Molecular mechanisms of action. *Environment International* 83:11–40; doi:10.1016/j.envint.2015.05.012. [PubMed: 26073844]
- Klebanoff MA, Keim SA. 2011 Epidemiology: the changing face of preterm birth. *Clin Perinatol* 38:339–350; doi:10.1016/j.clp.2011.06.006. [PubMed: 21890013]
- Lassen TH, Frederiksen H, Kyhl HB, Swan SH, Main KM, Andersson A-M, et al. 2016 Prenatal Triclosan Exposure and Anthropometric Measures Including Anogenital Distance in Danish Infants. *Environ Health Perspect* 124:1–8; doi:10.1289/ehp.1409637. [PubMed: 26058085]
- Lee B-E, Park H, Hong Y-C, Ha M, Kim Y, Chang N, et al. 2014 Prenatal bisphenol A and birth outcomes: MOCEH (Mothers and Children's Environmental Health) study. *International Journal of Hygiene and Environmental Health* 217:328–334; doi:10.1016/j.ijheh.2013.07.005. [PubMed: 23911140]
- Liao C, Liu F, Alomirah H, Loi VD, Mohd MA, Moon H-B, et al. 2012 Bisphenol S in Urine from the United States and Seven Asian Countries: Occurrence and Human Exposures. *Environ. Sci. Technol* 46:6860–6866; doi:10.1021/es301334j. [PubMed: 22620267]
- Mancini FR, Paul D, Gauvreau J, Volatier JL, Vin K, Hulin M. 2015 Dietary exposure to benzoates (E210–E213), parabens (E214–E219), nitrites (E249–E250), nitrates (E251–E252), BHA (E320), BHT (E321) and aspartame (E951) in children less than 3 years old in France. *Food Additives & Contaminants: Part A* 32:293–306; doi:10.1080/19440049.2015.1007535.
- Martin JA, Hamilton BE, Osterman MJK. 2017 Births in the United States, 2016. *NCHS Data Brief* 1–8.
- McElrath TF, Hecht JL, Dammann O, Boggess K, Onderdonk A, Markenson G, et al. 2008 Pregnancy Disorders That Lead to Delivery Before the 28th Week of Gestation: An Epidemiologic Approach to Classification. *American Journal of Epidemiology* 168:980–989; doi:10.1093/aje/kwn202. [PubMed: 18756014]
- Meeker JD, Cantonwine DE, Rivera-González LO, Ferguson KK, Mukherjee B, Calafat AM, et al. 2013 Distribution, Variability, and Predictors of Urinary Concentrations of Phenols and Parabens among Pregnant Women in Puerto Rico. *Environ. Sci. Technol* 47:3439–3447; doi:10.1021/es400510g. [PubMed: 23469879]

- Meeker JD, Hu H, Cantonwine DE, Lamadrid-Figueroa H, Calafat AM, Ettinger AS, et al. 2009 Urinary Phthalate Metabolites in Relation to Preterm Birth in Mexico City. *Environ Health Perspect* 117:1587–1592; doi:10.1289/ehp.0800522. [PubMed: 20019910]
- Miao M, Yuan W, Zhu G, He X, Li D-K. 2011 In utero exposure to bisphenol-A and its effect on birth weight of offspring. *Reprod. Toxicol* 32:64–68; doi:10.1016/j.reprotox.2011.03.002. [PubMed: 21440056]
- Mortensen ME, Calafat AM, Ye X, Wong L-Y, Wright DJ, Pirkle JL, et al. 2014 Urinary concentrations of environmental phenols in pregnant women in a pilot study of the National Children's Study. *Environmental Research* 129:32–38; doi:10.1016/j.envres.2013.12.004. [PubMed: 24529000]
- Moster D, Lie RT, Markestad T. 2008 Long-term medical and social consequences of preterm birth. *N Engl J Med* 359:262–273; doi:10.1056/NEJMoa0706475. [PubMed: 18635431]
- Nijman TAJ, van Vliet EOG, Benders MJN, Mol Ben Willem J, Franx A, Nikkels PGJ, et al. 2016 Placental histology in spontaneous and indicated preterm birth: A case control study. *Placenta* 48:56–62; doi:10.1016/j.placenta.2016.10.006. [PubMed: 27871473]
- Philippat C, Mortamais M, Chevrier C, Petit C, Calafat AM, Ye X, et al. 2012 Exposure to phthalates and phenols during pregnancy and offspring size at birth. *Environ Health Perspect* 120:464–470; doi:10.1289/ehp.1103634.
- Rahman A, Kumarathasan P, Gomes J. 2016 Infant and mother related outcomes from exposure to metals with endocrine disrupting properties during pregnancy. *Sci. Total Environ.* 569–570:1022–1031; doi:10.1016/j.scitotenv.2016.06.134.
- Ramaswamy BR, Kim J-W, Isobe T, Chang K-H, Amano A, Miller TW, et al. 2011 Determination of preservative and antimicrobial compounds in fish from Manila Bay, Philippines using ultra high performance liquid chromatography tandem mass spectrometry, and assessment of human dietary exposure. *Journal of Hazardous Materials* 192:1739–1745; doi:10.1016/j.jhazmat.2011.07.006. [PubMed: 21798664]
- Reijnders IF, Mulders AGMGJ, Koster MPH. 2017 Placental development and function in women with a history of placenta-related complications: a systematic review. *Acta Obstet Gynecol Scand* 261:412–10; doi:10.1111/aogs.13259.
- Rochester JR, Bolden AL. 2015 Bisphenol S and F: A Systematic Review and Comparison of the Hormonal Activity of Bisphenol A Substitutes. *Environ Health Perspect* 1–9; doi:10.1289/ehp.1408989.
- Rosner BBA. 2011 Fundamentals of biostatistics. Seventh edition Boston: Brooks/Cole, Cengage Learning, 2011.
- Schoen CN, Tabbah S, Iams JD, Caughey AB, Berghella V. 2015 Why the United States preterm birth rate is declining. *American Journal of Obstetrics and Gynecology* 213:175–180; doi:10.1016/j.ajog.2014.12.011. [PubMed: 25511243]
- Snijder CA, Heederik D, Pierik FH, Hofman A, Jaddoe VW, Koch HM, et al. 2013 Fetal Growth and Prenatal Exposure to Bisphenol A: The Generation R Study. *Environ Health Perspect* 121; doi: 10.1289/ehp.1205296.
- Tang R, Chen M-J, Ding G-D, Chen X-J, Han X-M, Zhou K, et al. 2013a Associations of prenatal exposure to phenols with birth outcomes. *Environmental Pollution* 178:115–120; doi:10.1016/j.envpol.2013.03.023. [PubMed: 23562958]
- Tang R, Chen M-J, Ding G-D, Chen X-J, Han X-M, Zhou K, et al. 2013b Associations of prenatal exposure to phenols with birth outcomes. *Environmental Pollution* 178:115–120; doi:10.1016/j.envpol.2013.03.023. [PubMed: 23562958]
- Thomas JD, Hultquist RA. 1978 Interval Estimation for the Unbalanced Case of the One-Way Random Effects Model. *Ann. Statist* 6:582–587; doi:10.1214/aos/1176344202.
- Thompson PA, Khatami M, Baglolle CJ, Sun J, Harris SA, Moon E-Y, et al. 2015 Environmental immune disruptors, inflammation and cancer risk. *CARCIN* 36:S232–S253; doi:10.1093/carcin/bgv038.
- Troisi J, Mikelson C, Richards S, Symes S, Adair D, Zullo F, et al. 2014 Placental concentrations of bisphenol A and birth weight from births in the Southeastern U.S. *Placenta* 35:947–952; doi: 10.1016/j.placenta.2014.08.091. [PubMed: 25227326]

- Vandenberg LN, Hauser R, Marcus M, Olea N, Welshons WV. 2007 Human exposure to bisphenol A (BPA). *Reproductive Toxicology* 24:139–177; doi:10.1016/j.reprotox.2007.07.010. [PubMed: 17825522]
- Wan Y, Huo W, Xu S, Zheng T, Bin Zhang, Li Y, et al. 2018 Relationship between maternal exposure to bisphenol S and pregnancy duration. *Environmental Pollution* 238:717–724; doi:10.1016/j.envpol.2018.03.057. [PubMed: 29621731]
- Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, et al. 2008 Prenatal Phenol and Phthalate Exposures and Birth Outcomes. *Environ Health Perspect* 116:1092–1097; doi:10.1289/ehp.11007. [PubMed: 18709157]
- Wolff MS, Pajak A, Pinney SM, Windham GC, Galvez M, Rybak M, et al. 2017 Associations of urinary phthalate and phenol biomarkers with menarche in a multiethnic cohort of young girls. *Reproductive Toxicology* 67:56–64; doi:10.1016/j.reprotox.2016.11.009. [PubMed: 27851993]
- Wu C, Huo W, Li Y, Bin Zhang, Wan Y, Zheng T, et al. 2017 Maternal urinary paraben levels and offspring size at birth from a Chinese birth cohort. *Chemosphere* 172:29–36; doi:10.1016/j.chemosphere.2016.12.131. [PubMed: 28061343]
- Ye X, Wong L-Y, Kramer J, Zhou X, Jia T, Calafat AM. 2015 Urinary Concentrations of Bisphenol A and Three Other Bisphenols in Convenience Samples of U.S. Adults during 2000–2014. *Environ. Sci. Technol* 49:11834–11839; doi:10.1021/acs.est.5b02135. [PubMed: 26360019]
- Ye X, Wong L-Y, Zhou X, Calafat AM. 2014 Urinary Concentrations of 2,4-Dichlorophenol and 2,5-Dichlorophenol in the U.S. Population (National Health and Nutrition Examination Survey, 2003–2010): Trends and Predictors. *Environ Health Perspect* 1–5; doi:10.1289/ehp.1306816.

Highlights

- We measured ten unique phenol compounds in this case-control study of preterm birth
- Ethyl paraben was associated with increased risk for placental preterm birth
- 2,5-Dichlorophenol was associated with decreased risk for overall preterm birth
- A majority of the phenols were not associated with birth outcomes

Figure 1.

Odds ratios for overall preterm birth in relation to individual phenols and parabens. Logistic regression models are adjusted for specific gravity at each study visit, maternal age (continuous), maternal race (categorical), pre-pregnancy BMI (continuous), insurance provider (categorical), maternal education level (categorical). Abbreviations: 2,4-dichlorophenol (2,4-DCP); 2,5-dichlorophenol (2,5-DCP); benzophenone-3 (BP3); triclosan (TCS); bisphenol-S (BPS); triclocarban (TCB). *BPS and TCB are modeled as categorical variables (detected in any of the repeated samples vs. all non-detect)

Table 1.

Population characteristics of the LIFECODES study (N=480)

		Preterm [N(%)]	Term [N(%)]
Age	Median (range)	32.7 (20.9–50.2)	31.9 (18.3–48.7)
	<25	9 (6.9)	44 (12.6)
	25–30	27 (20.8)	68 (19.4)
	30–35	53 (40.8)	136 (38.9)
	>35	41 (31.5)	102 (29.1)
Race/ethnicity	White	74 (56.9)	208 (59.4)
	African American	24 (18.5)	53 (15.1)
	Other	32 (24.6)	89 (8.3)
Pre-pregnancy BMI	Median	24.8 (16.6–45.2)	24.0 (16.9–51.5)
	< 25 kg/m ²	64 (49.2)	195 (55.7)
	25–30 kg/m ²	32 (24.6)	88 (25.1)
	>30 kg/m ²	30 (23.1)	60 (17.1)
	Missing	4 (3.1)	7 (2.0)
Health insurance	Public	20 (15.4)	70 (20.0)
	Private	108 (83.1)	270 (77.1)
	Missing	2 (1.5)	10 (2.9)
Education	High school	20 (15.4)	47 (13.4)
	Technical school	25 (19.2)	52 (14.9)
	Junior/some college	38 (29.2)	100 (28.6)
	College graduate	46 (35.4)	141 (40.3)
	Missing	1 (0.8)	10 (2.9)
Fetal sex	Female	57 (43.9)	156 (44.6)
	Male	73 (56.2)	194 (55.4)
ART	No	116 (89.2)	312 (89.1)
	Yes	14 (10.8)	38 (10.9)
IVF	No	120 (92.3)	329 (94.0)
	Yes	10 (7.7)	21 (6.0)
Nulliparous	No	75 (57.7)	192 (54.9)
	Yes	55 (42.3)	158 (45.1)
Gravid	No	32 (24.6)	110 (31.4)
	Yes	98 (75.4)	240 (68.6)
Tobacco use	No	120 (92.3)	332 (94.9)
	Yes	10 (7.7)	18 (5.1)
Alcohol use	No	126 (96.9)	324 (92.6)
	Yes	1 (0.8) *	19 (5.4) *
	Missing	3 (2.3)	7 (2.0)

*
P-value <0.05 for ANOVA

Abbreviations: Body mass index (BMI); Assisted reproductive technology (ART); *In-vitro* fertilization (IVF)

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Table 2.

Distribution of specific gravity-corrected phenols and parabens in urine (ng/ml). N=1,647.

Analyte	Percentiles						
	LOD	N (%) <LOD	25 th	50 th	75 th	90 th	95 th
2,4-DCP	0.2	306 (18.5)	0.3	0.7	1.5	4.0	8.0
2,5-DCP	0.2	62 (3.7)	1.2	3.1	10.9	51.7	162
BP3	0.4	5 (0.3)	9.6	39.3	237	1263	2741
BPS	0.4	1313 (79.4)	< LOD	< LOD	< LOD	1.2	2.10
Butyl Paraben	0.2	523 (31.6)	< LOD	0.8	6.0	21.4	38.2
Ethyl Paraben	1.0	670 (40.5)	< LOD	2.1	13.1	53.5	99.9
Methyl Paraben	1.0	2 (0.1)	58.6	168	440	982	1760
Propyl Paraben	0.2	17 (1.0)	11.7	42.1	121	282	491
TCB	2.0	1533 (92.7)	< LOD	< LOD	< LOD	< LOD	10.1
TCS	2.0	339 (20.5)	3.0	10.3	59.6	291	497

Abbreviations: 2,4-dichlorophenol (2,4-DCP); 2,5-dichlorophenol (2,5-DCP); benzophenone-3 (BP3); bisphenol-S (BPS); triclocarban (TCB); triclosan (TCS); limit of detection (LOD)

Table 3.Intraclass correlation coefficients and 95% confidence intervals. N=1,647^a

	Uncorrected		Specific gravity-corrected	
	ICC	95% CI	ICC	95% CI
2,4-DCP	0.53	0.49, 0.58	0.47	0.42, 0.51
2,5-DCP	0.70	0.66, 0.73	0.65	0.61, 0.68
BP3	0.55	0.50, 0.59	0.58	0.54, 0.63
Butyl Paraben	0.47	0.42, 0.52	0.51	0.46, 0.55
Ethyl Paraben	0.50	0.45, 0.54	0.52	0.47, 0.57
Methyl Paraben	0.50	0.45, 0.55	0.49	0.44, 0.54
Propyl Paraben	0.46	0.41, 0.51	0.46	0.41, 0.51
TCS	0.49	0.44, 0.54	0.51	0.46, 0.56
Specific gravity	0.38	0.33, 0.43	-	-

^aSample total from four study visits (median gestational weeks): visit 1 (9.7 weeks); visit 2 (17.9 weeks); visit 3 (26 weeks); visit 4 (35 weeks).

Abbreviations: 2,4-dichlorophenol (2,4-DCP); 2,5-dichlorophenol (2,5-DCP); Benzophenone-3 (BP3); Triclosan (TCS)

Table 4.

Adjusted odds ratios of preterm birth and subtypes in association with phenols and parabens in three model types: single pollutant models (Type 1), multi-pollutant model with co-adjustment of mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) (Type 2), and multi-pollutant model with co-adjustment of predictors associated from single pollutant models (Type 3).

N (cases, controls)	Overall (122,332)		Spontaneous (71,332)		Placental (33, 332)	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Model Type 1						
2,4-DCP	0.87 (0.70, 1.10)	0.24	0.80 (0.60, 1.08)	0.14	1.0 (0.65, 1.46)	0.99
2,5-DCP	0.79 (0.67, 0.94)	0.01	0.81 (0.66, 0.99)	0.04	0.73 (0.52, 0.99)	0.05
BPS *	0.92 (0.59, 1.45)	0.73	0.84 (0.48, 1.47)	0.54	1.08 (0.47, 2.46)	0.86
BP3	0.99 (0.87, 1.12)	0.85	0.99 (0.85, 1.15)	0.87	1.08 (0.86, 1.35)	0.50
Butyl Paraben	1.00 (0.87, 1.14)	0.94	0.95 (0.80, 1.12)	0.52	1.06 (0.83, 1.34)	0.63
Ethyl Paraben	1.04 (0.90, 1.20)	0.59	0.89 (0.73, 1.07)	0.20	1.47 (1.14, 1.91)	0.004
Methyl Paraben	1.15 (0.95, 1.38)	0.15	1.14 (0.91, 1.44)	0.26	1.12 (0.80, 1.59)	0.51
Propyl Paraben	1.05 (0.90, 1.22)	0.56	1.02 (0.84, 1.23)	0.83	1.08 (0.82, 1.44)	0.61
TCS	0.97 (0.85, 1.11)	0.69	0.84 (0.70, 1.0)	0.05	1.05 (0.83, 1.34)	0.66
TCB *	0.77 (0.40, 1.49)	0.43	0.93 (0.42, 2.06)	0.86	0.42 (0.10, 1.69)	0.22
Model Type 2						
2,4-DCP	0.88 (0.69, 1.09)	0.26	0.81 (0.59, 1.07)	0.16	1.0 (0.65, 1.47)	0.99
2,5-DCP	0.79 (0.66, 0.93)	0.01	0.8 (0.65, 0.98)	0.04	0.73 (0.51, 0.99)	0.05
BPS *	0.87 (0.55, 1.37)	0.56	0.77 (0.43, 1.34)	0.35	1.05 (0.45, 2.41)	0.90
BP3	0.98 (0.86, 1.11)	0.77	0.98 (0.84, 1.15)	0.83	1.07 (0.85, 1.34)	0.57
Butyl Paraben	1.0 (0.87, 1.14)	0.95	0.94 (0.80, 1.11)	0.49	1.07 (0.83, 1.35)	0.60
Ethyl Paraben	1.04 (0.9, 1.2)	0.61	0.88 (0.72, 1.05)	0.18	1.48 (1.14, 1.93)	0.003
Methyl Paraben	1.15 (0.95, 1.39)	0.15	1.14 (0.91, 1.45)	0.26	1.13 (0.80, 1.60)	0.50
Propyl Paraben	1.05 (0.9, 1.23)	0.51	1.03 (0.85, 1.25)	0.80	1.08 (0.82, 1.45)	0.58
TCS	0.97 (0.84, 1.11)	0.63	0.83 (0.69, 0.99)	0.04	1.05 (0.83, 1.34)	0.67
TCB *	0.75 (0.37, 1.43)	0.40	0.91 (0.39, 1.95)	0.81	0.41 (0.08, 1.45)	0.22
Model Type 3						
2,5-DCP	0.79 (0.67, 0.93)	0.006	0.81 (0.65, 0.98)	0.04	0.69 (0.48, 0.95)	0.031
Ethyl Paraben	1.05 (0.9, 1.2)	0.54	0.89 (0.73, 1.07)	0.22	1.5 (1.16, 1.97)	0.003
TCS	0.97 (0.85, 1.11)	0.71	0.84 (0.69, 0.99)	0.05	1.07 (0.83, 1.36)	0.61

Adjusted for average specific gravity, age (continuous), race (categorical), prepregnancy BMI (continuous), insurance provider (categorical), education level (categorical).

Abbreviations: 2,4-dichlorophenol (2,4-DCP); 2,5-dichlorophenol (2,5-DCP); benzophenone-3 (BP3); triclosan (TCS); bisphenol-S (BPS); triclocarban (TCB)

* BPS and TCB modeled as categorical (detected in any of the repeated samples vs. all non-detected)