Prenatal urinary concentrations of phenols and risk of preterm birth: exploring windows of vulnerability

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Objective: To explore windows of vulnerability to prenatal urinary phenol concentrations and preterm birth.
Design: Prospective cohort.
Setting: A large fertility center in Boston, Massachusetts.
Patient(s): A total of 386 mothers who sought fertility treatment and gave birth to a singleton between 2005 and 2018.
Intervention(s): None.
Main outcome measure(s): Singleton live birth with gestational age <37 completed weeks.
Result(s): Compared with women with non-preterm births, urinary bisphenol A (BPA) concentrations were higher across gestation among women with preterm births, particularly during mid-to-late pregnancy and among those with female infants. Second trimester BPA concentrations were associated with preterm birth (Risk Ratio [RR] 1.24; 95%CI: 0.92, 1.69), which was primarily driven by female (RR 1.40; 95%CI: 1.04, 1.89) and not male (RR 0.85; 95%CI 0.50, 1.46) infants. First trimester paraben concentrations were also associated with preterm birth (RR 1.17; 95%CI: 0.94, 1.46) and similarly the association was only observed for female (RR 1.46; 95% CI: 1.10, 1.94) and not male infants (RR 0.94; 95%CIC: 0.72, 1.23). First trimester urinary bisphenol S concentrations showed a suggested risk of preterm birth (RR 1.25; 95%CI: 0.82, 1.89), although the small case numbers precluded sex-specific examination.
Conclusion(s): We found preliminary evidence of associations between mid-to-late pregnancy BPA and early pregnancy paraben concentrations with preterm birth among those with female infants only. Preterm birth risk may be compound, sex, and window specific. Given the limited sample size of this cohort, results should be confirmed in larger studies, including fertile populations. (Fertil Steril® 2021;116:820-32. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Bisphenol A, phenols, pregnancy, preterm birth

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Prenatal exposure to endocrine-disrupting chemicals is an increasingly recognized risk factor for adverse pregnancy outcomes, including preterm birth (1–8). Birth before 37 completed weeks of gestation is considered one of the strongest predictors of infant morbidity and mortality (9–12). Although numerous risk factors have been identified, including multiple gestations, intrauterine infection, and conditions such as diabetes and hypertension in pregnancy, the

underlying causes of preterm birth remain largely unknown (13, 14).

Endocrine-disrupting chemicals are defined as exogenous chemicals, or mixtures of chemicals, that may interfere with any aspect of hormone action (15). Among them, phenols constitute a broad chemical family that share structural similarities. Phenols are widely used in food packaging materials, personal care products, and numerous other consumer products (16–20), resulting in ubiquitous exposure (21, 22). Bisphenols, benzophenones, triclosan, and parabens are among the most studied phenols because of concerns about their endocrine active properties and their widespread population exposure (17, 23–32).

Phenols such as bisphenol A (BPA), triclosan, and benzophenone-3 were shown in rodent models to exert adverse effects, including alterations in uterine arterial remodeling, and on decidualization, implantation, placental development, and intrauterine growth restriction (33–36). Although these disruptions may increase the preterm birth risk, rodent studies constitute an inadequate experimental model (2). Human studies are thus needed to investigate the environmental influences on preterm birth. A limited number of studies have examined the associations between prenatal phenol exposure and preterm birth (24, 37–41). The findings were inconsistent, possibly because of the heterogeneity in study design and the timing of exposure assessment (24, 37–41). Most previous studies assessed phenol exposure at a single pregnancy time-point, for example, in the second (24) or third (39) trimester, or just before delivery (40, 41). These studies failed to account for the high variability of phenol exposure across pregnancy and the potentially different periods of vulnerability during pregnancy (2, 42, 43). Exploring windows of exposure across pregnancy can suggest pathways of adverse effects of phenols on preterm birth (2). First trimester exposure may interfere with implantation or placentation, which may result in subsequent preterm delivery (33, 34, 36). Second trimester exposure might disrupt the metabolic adaptation of mothers and nutrition transfer to fetuses, resulting in fetal growth restriction, preeclampsia, glucose intolerance, or other metabolic diseases (35), which are direct risk factors for preterm birth. Third trimester exposure may be related to increasing triggers for preterm delivery such as inflammation and the cytokine cascade needed to trigger labor (44, 45).

To date, only two studies have examined repeated measurements across trimesters: a nested case-control study from the LIFECODES cohort in Boston, Massachusetts (38, 46) and a prospective cohort in China (38). The case-control study examined phenol concentrations from four prenatal visits in relation to preterm birth. The investigators found that urinary BPA and BPS concentrations at the fourth visit were associated with higher odds of preterm birth (38, 46). As with all preterm birth studies, the findings in the third trimester may be influenced by selection bias as women delivering early would fail to attend the fourth visit and thus not be included in the case ascertainment. The Chinese cohort observed that prenatal urinary BPA concentrations, especially in the second and third trimesters, were associated with higher odds of preterm birth. However, pregnancies in this Chinese cohort were possibly at lower risk overall given only 2.5% of the births ended preterm. Thus, the findings may not be informative to the general population (37). In addition, several studies suggested that infant sex may modify the association between prenatal phenol exposure and preterm birth, but the evidence is limited and inconclusive (24, 38). In this prospective preconception cohort of subfertile couples, we aimed to investigate the association of prenatal urinary phenol concentrations and the risk of preterm birth, exploring the timing of vulnerability across gestational windows and the potential modification by infant sex.

MATERIALS AND METHODS

Study Cohort

The Environment and Reproductive Health (EARTH) Study is a prospective preconception cohort of heterosexual couples seeking fertility care and treatment at the Massachusetts General Hospital Fertility Center. The aim of this study is to investigate how environmental and nutritional exposures in both men and women influence fertility, gestation, and neonatal outcomes. Detailed information on the EARTH cohort profile can be found elsewhere (47). In brief, women and men were invited to participate independently or as a couple and were followed from study entry through their fertility care, pregnancy, and delivery. Participants completed general and lifestyle questionnaires, underwent anthropometric measurements, and provided a spot urine and blood sample at baseline and at each fertility treatment cycle as well as across gestation among women achieving conception.

The present study included 386 mothers participating in the EARTH Study who gave birth to a singleton infant between 2005 and 2018 and who had at least one urine sample quantified for phenol biomarkers during pregnancy (Supplemental Fig. 1, available online). A total of 956 urine samples were collected. Study details were explained to all participants by trained study staff, and all participants signed informed consent. This study was approved by the Institutional Review Boards of Massachusetts General Hospital, Harvard T.H. Chan School of Public Health, and the Centers for Disease Control and Prevention.

Exposure Biomarker Assessment

Pregnant women collected one spot urine sample at early, middle, and late pregnancy (median sample collection time for the first sample: 6 weeks, the second sample: 21 weeks, the third sample: 34 weeks) of the index pregnancy using sterile polypropylene cups. Urine was analyzed for specific gravity (SG) with a handheld or Atago PAL-10S refractometer (National Instrument Company, Inc., Baltimore, MD), divided into aliquots, and frozen for long-term storage at −80°C. Aliquots were shipped on dry ice overnight to the Centers for Disease Control and Prevention (Atlanta, GA) for quantification of bisphenol A (BPA), bisphenol S (BPS), methylparaben, ethylparaben, propylparaben, butylparaben, benzophenone-3, and triclosan using solid-phase extraction coupled with high-performance liquid chromatography-isotope dilution tandem mass spectrometry (48). The limits of detection (LODs) ranged from 0.1 to 1.0 ng/mL. Because the detection

rate for ethylparaben was low (30%), we did not include this biomarker in further analyses. We calculated the sum of the parabens by dividing each paraben concentration by its molecular weight, summing the individual molar concentrations, and then multiplying the resulting sum by the molecular weight of methylparaben (152.15) to convert the molar concentration to ng/mL units (49):

$$\sum Parabens = 152.15\,[(Methylparaben*(1/152.15)) + (Propylparaben*(1/180.20)) + (Butylparaben*(1/194.23))].$$

Outcome Assessment

Gestational age in days was abstracted from the delivery records and validated using the American College of Obstetricians and Gynecologists guidelines for estimating gestational age of births after medically assisted reproduction (50). For in vitro fertilization (IVF) pregnancies, we estimated the gestational age by (outcome date − transfer date + 14 days + cycle day of transfer) (50). For intrauterine insemination and nonmedically assisted/naturally conceived pregnancies, we used (birth date − cycle start date). Gestational age was corrected if delivery record estimates (gold standard) differed from the clinically estimated age by >6 days through additional chart verification (corrected for three infants). Preterm birth was defined as any live birth <37 completed weeks of gestation (<259 days).

Covariates

Maternal age, race, education, parity, and smoking status were obtained from self-reported baseline questionnaires. Study staff measured participant height and weight at study entry. Body Mass Index (BMI) (kg/m^2) was calculated as weight in kilograms divided by height in meters squared. The cause of infertility was diagnosed by the physician administering the fertility treatment using the Society for Assisted Reproductive Technology definitions (51, 52). The type of medically assisted reproduction used in the conception cycle of the index birth was obtained from electronic medical records by trained study staff, which was dichotomized as assisted reproductive technology (ART) procedures (e.g., fresh or frozen IVF protocols, including intracytoplasmic sperm injection) vs. non-ART protocols (e.g., intrauterine insemination with or without ovulation induction/stimulation; ovulation induction/stimulation with timed intercourse, or nonmedically assisted/naturally conceived).

Statistical Analysis

Maternal and birth characteristics were reported using means (SD) or number (percent). Trimester-specific urinary phenol concentrations were estimated based on the gestational week when the urine sample was collected. Phenol biomarker concentrations below the LOD were assigned the LOD divided by the square root of 2 (53). Each phenol biomarker concentration was multiplied by [(SGp-1)/(SGi-1)] to account for urinary dilution, where SGi was the specific gravity of the participant's urine sample and SGp was the mean specific gravity for all female participants (mean = 1.014) included in the study samples (54). The SG-adjusted biomarker concentrations were natural log-transformed to minimize the skewness of the distribution and reduce the influence of extreme values. We calculated descriptive statistics for biomarker concentrations and the percentages of concentrations below the LOD. Spearman correlation coefficients were calculated using natural log-transformed phenol biomarker concentrations to assess the correlations between measures of the same phenol biomarker concentrations across trimesters. To assess the temporal variability of the prenatal phenol concentrations by participant, intraclass correlation coefficients (ICCs) were calculated using mixed effects models. The ICC is calculated as the ratio of the between-subject variance to the sum of the between- and within-subject variances. It ranges from 0 to 1, with 1 indicating no within-subject variance.

Covariates were selected a priori based on substantive knowledge using a directed acyclic graph (Supplemental Fig. 2, available online). Predictors of both phenol exposure and preterm birth were adjusted for in the model. Covariates included: maternal age and BMI (continuous) as potential predictors of both the exposure and outcome (55, 56), maternal education (<college, college, graduate degree) as an indicator of socioeconomic status, smoking status (never smoked vs. ever smoked defined as a current or former smoker) given its relationship with the outcome (57) and its potential interference with phenols metabolism and excretion (58), race (Caucasian, Black or African American, Asian, Other) to account for genetic or social disparities (59), and ART vs. non-ART-based treatment (60).

Methodological Approaches

To explore the period of vulnerability to phenol exposure on preterm birth across gestation, we applied two methodological approaches to examine the trimester-specific phenol biomarker concentrations as predictors of preterm birth and the relative biomarker concentrations across gestation comparing preterm and non-preterm births. We further stratified the analyses by infant sex to explore effect modification by sex of the observed associations.

Approach 1—trimester-specific associations. We fit multiple informant models for continuous urinary phenol biomarker concentrations at each of the three trimesters in relation to preterm birth. In brief, multiple informant models treat each of the three trimesters as informants and simultaneously estimate the association between biomarker concentrations and preterm birth for each trimester. This method retains the interpretation of a set of separate regressions for each trimester while also testing the difference in associations between urinary phenol biomarker concentrations and preterm birth across trimesters using Type 3 tests (61). Given our small sample size and the concern that test of heterogeneity is often underpowered to detect significant differences at the traditional .05 cutoff P value, we considered a Type 3 P value of <.20 as an indication that the associations may differ across trimesters. We used generalized estimating equations with a log link function and Poisson distribution to estimate risk ratios (RRs) and 95%CIs of preterm birth for each

natural log-unit increase in phenol biomarker concentration per trimester. We fit unadjusted and covariate-adjusted models for each phenol biomarker of interest.

Approach 2—relative phenol biomarker concentrations comparing preterm and non- preterm births. To further assess windows of vulnerability to phenol exposure across pregnancy, we used a similar approach as that described by Sanchez and colleagues (61). This approach does not prespecify vulnerable windows per se (i.e., trimesters) but rather compares exposure patterns across gestational weeks among women who had a preterm birth with those who delivered at term. To do so, we applied mixed models with linear and quadratic terms for gestational week to estimate patterns of urinary phenol biomarker concentrations (and corresponding 95% CIs) among preterm vs. non-preterm births across gestational weeks, adjusting for covariates.

Sensitivity analyses. We undertook several sensitivity analyses to assess the robustness of our findings. First, missing exposure assessment at any trimester may be informative of birth outcomes and thus could lead to potential selection bias. For example, women who had a preterm birth may not be available to provide urine samples later in pregnancy. To assess this, we restricted our multiple informant models to the 239 women who provided urine samples at all three trimesters and applied inverse probability weighting to account for potential selection bias because of missing data at any trimester (62, 63). The weights were the inverse of the predicted probabilities for women providing urine samples at every trimester. The probabilities were predicted using logistic models with covariates being possible predictors of providing urine samples at every trimester. The predictors included study year (continuous), maternal age (continuous), before pregnancy BMI (continuous), education (categorical), race/ethnicity (categorical), parity (binary), history of pregnancy loss (binary), paternal participation in the study (binary), preterm birth (binary), and a composite prenatal risk variable (categorical) that equaled 1 if the women had any of the following complications as were abstracted from medical records: diabetes (preexisting or gestational), hypertension (preexisting or gestational), preeclampsia, thrombophilia, placental abruption, cervical insufficiency, preterm labor or premature rupture of the membranes, or intrauterine growth restriction. Second, we fit Poisson regression models across phenol biomarker quartiles to explore the dose-response effects within positive findings and to confirm the assumption of linearity in the associations between log-transformed phenol biomarker concentrations and preterm birth in our primary models. The *P* value for the trend was obtained by assigning biomarker quartiles as an ordinal variable in the models. A cutoff of .20 for the *P* values was set as potential evidence of a linear trend across ordinal categories of the exposure of interest and preterm birth. Third, because the benzophenone-3 concentration may be influenced by seasonal sunscreen use, we further adjusted for the month of urine sample collection as a proxy for season in models of benzophenone-3. Statistical analyses were conducted with SAS (version 9.4; SAS Institute Inc., Cary, NC). Our interpretation of the results was based on the consistency of different models and consideration of both previously published epidemiologic studies and biologic plausibility criteria from experimental studies.

RESUTS

Study Cohort

The present study included 386 mothers with a mean (SD) age of 34.7 (3.9) years and a mean (SD) BMI of 24.2 (4.3) kg/m^2 (Table 1). Among the 386 singleton infants, mean (SD) gestational age was 39.4 (1.7) weeks, with 8% born preterm (n = 31). Mean (SD) birth weight was 3,352 (529) grams, with 4% (n = 16) of infants born low birth weight (<2,500 grams) (Table 1).

Urinary Phenol Biomarker Concentrations

The distributions of the SG-adjusted urinary concentrations of phenol biomarkers were examined by trimester

TABLE 1

Characteristics of 386 mothers and their singleton infants in the Environment and Reproductive Health (EARTH) Study (2005–2018).

Characteristic	Value
Maternal characteristics (N = 386)	
Age (y), mean (SD)	34.7 (3.9)
BMI (kg/m^2), mean (SD)	24.2 (4.3)
Age >35 y, no. (%)	158 (41)
BMI >25 kg/m^2, no. (%)	125 (32)
Race or ethnicity, no. (%)	
White	327 (85)
Black or African American	11 (3)
Asian	32 (8)
Other	16 (4)
Education, no. (%)	
No college	52 (13)
College graduate	127 (33)
Graduate degree	207 (54)
Smoking status, no. (%)	
Never	290 (75)
Ever (former or current)	96 (25)
Infertility diagnosis, no. (%)	
Male factor	97 (25)
Female factor	124 (32)
Unexplained	165 (43)
Primiparous, no. (%)	321 (83)
Singleton characteristics (N = 386)	
Gestational age at birth (wk)	
Mean (SD)	39.4 (1.7)
Min–max	31–42
Birthweight (g)	
Mean (SD)	3,352 (529)
Min–max	1,090– 5,040
Male, no. (%)	200 (52)
Low birthweight (<2,500 g), no. (%)	16 (4)
Preterm birth (<37 wk), no. (%)	31 (8)
Mode of conception, no. (%)	
ART [a]	219 (57)
Non-ART [b]	167 (43)

Note: ART = assisted reproductive technology; BMI = body mass index.
[a] ART includes fresh or frozen in vitro fertilization protocols, including intracytoplasmic sperm injection.
[b] Non-ART includes intrauterine insemination with or without ovulation induction/stimulation; ovulation induction/stimulation with timed intercourse, or non-medically-assisted/naturally conceived.

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(Supplemental Table 1, available online). Urinary biomarker concentrations across trimesters showed moderate-to-high detection frequencies. The lowest detection frequency was found for first trimester butylparaben (54%). The detection frequencies of phenol biomarkers were similar across trimesters (Supplemental Table 1). The second trimester SG-adjusted geometric mean benzophenone-3 concentration was 29% higher than that in the first trimester and 23% higher than that in the third trimester. First trimester SG-adjusted geometric mean ∑Paraben concentration was approximately 20% higher than that in the second and third trimesters (Supplemental Table 1). Moderate-to-high Spearman correlations were found for urinary ∑Parabens (r = 0.36–0.58), benzophenone-3 (r = 0.51–0.60), and triclosan (r = 0.52–0.70) concentrations across trimesters (Supplemental Table 2, available online). Other phenol biomarkers had relatively low correlations across trimesters (Supplemental Table 2). ICCs showed moderate temporal variability for ∑Parabens (ICC = 0.43), benzophenone-3 (ICC = 0.56), and triclosan (ICC = 0.58) (Supplemental Table 2). Other phenol biomarkers showed relatively low within-subject reproducibility across pregnancy (Supplemental Table 2).

Trimester-Specific Associations

Covariate-adjusted multiple informant models showed a suggestive positive association between second trimester urinary BPA concentrations and preterm birth (RR 1.24; 95%CI: 0.92, 1.69). This association was significant for female (RR 1.40; 95%CI: 1.04, 1.89) but not male infants (RR 0.85; 95%CI: 0.50, 1.46) (Fig. 1). Similarly, a positive association was found with third trimester urinary BPA concentrations and preterm birth among female infants (RR 1.91; 95%CI: 1.02, 3.58) but was null for male infants (RR 0.83; 95%CI: 0.36, 1.94). The association between first trimester urinary ∑Paraben concentrations was suggestive (RR 1.17; 95%CI: 0.94, 1.46) but positive for female (RR 1.46; 95%CI: 1.10, 1.94) and not male infants (RR 0.94; 95%CI: 0.72, 1.23).

First trimester urinary BPS concentrations were associated with a possible higher risk of preterm birth (RR 1.25; 95%CI: 0.82, 1.89) (Fig. 1). Because the sample size and number of preterm birth cases were small for BPS, we did not stratify the results by infant sex. Although individual associations within trimesters were identified, differences were not statistically significant across these windows: BPA (Type 3 P = .55), ∑Parabens (Type 3 P = .51), and BPS (Type 3 P = .50).

First trimester urinary benzophenone-3 concentrations were inversely associated with risk of preterm birth (RR 0.77; 95%CI: 0.57, 1.03), whereas associations were null for second and third trimesters (Type 3 P = .20) (Fig. 1). First trimester (RR 0.79; 95%CI: 0.66, 0.96) and third trimester (RR 0.77; 95%CI: 0.57, 1.06) urinary triclosan concentrations were also inversely associated with risk of preterm birth, with significant differences across trimesters (Type 3 P = .05) (Fig. 1). These inverse associations with benzophenone-3 and triclosan were mainly found among male infants in sex-stratified models (Fig. 1).

Relative Phenol Concentrations Comparing Preterm and Non-Preterm Births

Prenatal urinary BPA concentrations were higher among women with infants born preterm compared with those of women with infants born full term across gestational weeks, with some imprecision in confidence intervals (Fig. 2). This pattern of association was significant among women with female infants but not women with male infants from gestational weeks 21 to 29 (Fig. 3). No meaningful patterns of associations emerged among the other urinary phenol biomarker concentrations examined (Supplemental Figs. 3–6, available online).

Sensitivity Analysis

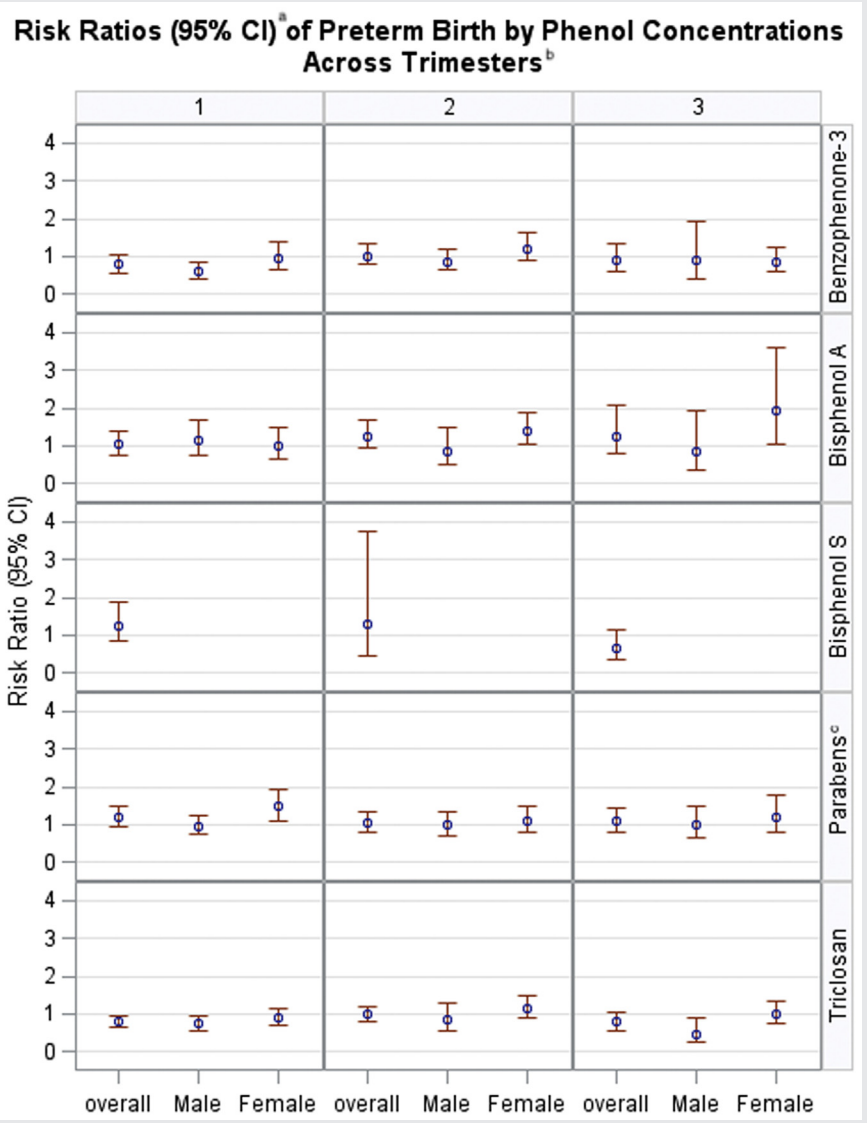
Trimester-specific findings were consistent with the primary analysis after restricting the sample to the 239 mothers who provided all three trimester urine samples using inverse probability weighting (Supplemental Table 3, available online). The association between second trimester BPA concentrations and preterm birth was strengthened and became significant in this restricted sample (RR 1.70; 95%CI: 1.22, 2.35). In analyses with biomarkers modeled as quartiles, we found suggestive nonlinear associations of first trimester ∑Paraben and second trimester BPA concentrations, with the highest RR of preterm birth at the fourth quartile, although with imprecise confidence intervals (Supplemental Table 4, available online). The BPS associations across quartiles were imprecise because of small numbers (Supplemental Table 4). Results for benzophenone-3 remained consistent with or without the inclusion of month of sample collection as a proxy for season as a covariate (Supplemental Table 5, available online).

DISCUSSION

In this prospective cohort of women attending a fertility clinic, we found suggestive positive associations between middle and late pregnancy BPA concentrations and preterm birth, especially among women carrying female fetuses. Mid-to-late pregnancy may be a potentially vulnerable period of risk for preterm birth in relation to BPA exposure, although imprecision may have precluded a firmer determination of this window. In support of this finding, we also reported that BPA concentrations were higher across all gestational weeks comparing mothers with and without infants born preterm, although CIs were again imprecise. Consistent with the multiple informant model analysis, sex-specific associations were found among female infants but not males, with a similar pattern of higher exposure across mid-pregnancy among women with infants born preterm. Restricting our sample to women providing all three urine samples and applying inverse probability weights strengthened our findings, suggesting possible differences among women providing complete exposure data. Triangulation of our results using two separate statistical methods showed consistency, counteracting the imprecision and potential selection bias issue of our study.

First trimester urinary ∑Paraben concentrations were associated with a higher risk of preterm birth, especially

FIGURE 1



Adjusted risk ratios (RR) and 95% CIs for preterm birth (<37 weeks) per log-unit increase in urinary phenol concentrations by trimester of pregnancy and infant sex among 386 mothers in the Environment and Reproductive Health (EARTH) Study (2005–2018). Urine sample sizes: ∑parabens = 355 (first trimester), 290 (second trimester), 299 (third trimester); bisphenol A = 361 (first trimester), 296 (second trimester), 299 (third trimester); benzophenone-3 = 249 (first trimester), 207 (second trimester), 210 (third trimester); triclosan = 249 (first trimester), 207 (second trimester), 210 (third trimester). [a] All models except bisphenol S (BPS) were adjusted for age (continuous), body mass index (continuous), assisted reproductive technology (yes/no), smoking (ever/never), education (no college, college, graduate degree), race or ethnicity (White, Black or African American, Asian, other). Models for BPS were not adjusted for smoking (ever/never) for convergence issue. [b] Type 3 *P* values for overall analyses: bisphenol A =.55, ∑parabens = .51, bisphenol S = .50, benzophenone-3 = .20, triclosan = .05. Type 3 *P* values <.20 were considered suggestive of differences among the associations across trimesters. [c] ∑parabens: the molar sum of parabens was estimated by dividing each concentration by its molecular weight and then summing: ∑parabens = [(methylparaben*(1/152.15)) + (propylparaben*(1/180.20)) + (butylparaben*(1/194.23))]. We then multiplied the molar sum by the molecular weight of methylparaben (152.15 g/mol) to express ∑parabens in ng/mL.

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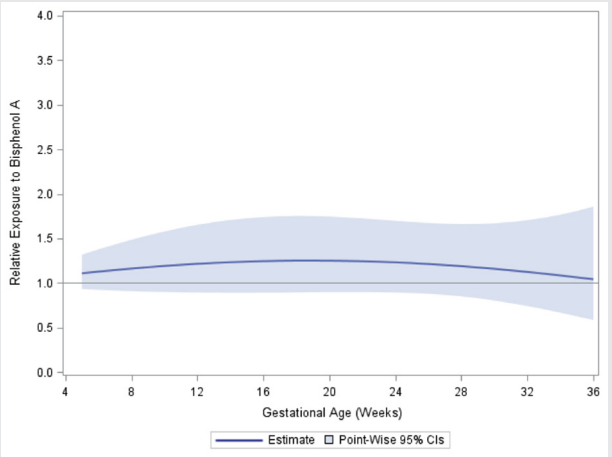
among female infants. Protective associations with first trimester bezonphenone-3 and first and third trimester triclosan concentrations and preterm birth were also detected. We did not observe any meaningful differences in biomarkers concentration distributions across gestational weeks comparing preterm and non-preterm births using quadratic mixed models for parabens, benzophenone-3, or triclosan.

In this study, the intraclass correlation coefficients were low for BPA and BPS and moderate for parabens and benzophenone-3 across gestation, which is consistent with previous studies (43, 64, 57). The high variability of

FIGURE 2



Relative bisphenol A concentrations across gestation comparing preterm and non-preterm births. Models were adjusted for age (continuous), body mass index (continuous), assisted reproductive technology (yes/no), smoking (ever/never), education (no college, college, graduate degree), and race or ethnicity (White, Black or African American, Asian, other). Data for Figure 2 was presented in Supplemental Table 6, available online.

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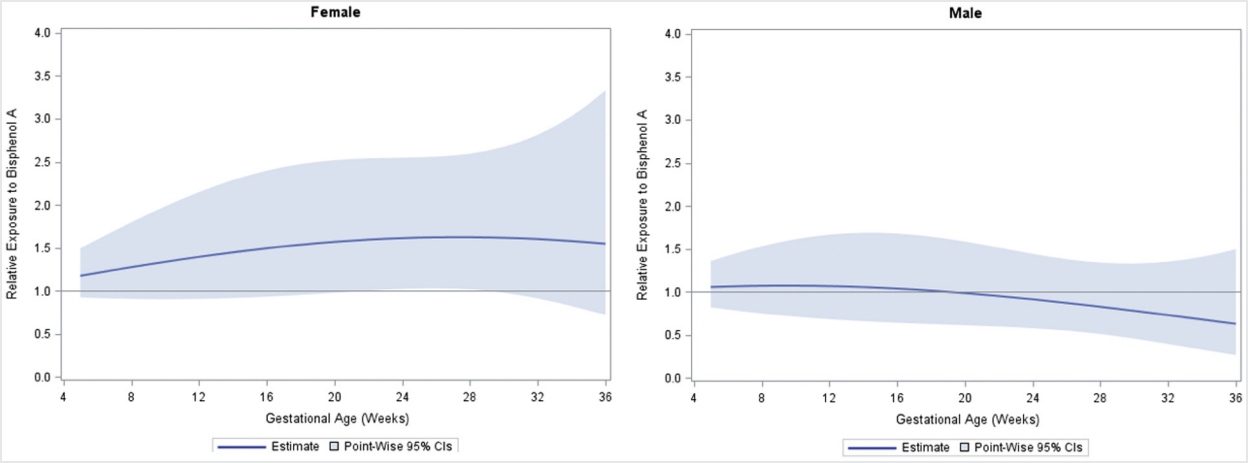
bisphenols and the moderate variability of the remaining phenols may be attributed to differences in lifestyles linked to personal care product use, diet, and other behaviors; however, it may also represent changes in metabolism during pregnancy.

Our finding that mid-to-late pregnancy BPA exposure was positively associated with the risk of preterm birth among female infants is compatible with several previous studies. Importantly, a nested case-control study in Boston, Massachusetts, reported a consistent fetus sex modification as in our study. Cantonwine et al. (38) found mean prenatal urinary BPA concentration was associated with the risk of preterm birth only among female infants. Furthermore, they observed urinary BPA concentrations at the early-to-middle second trimester and late third trimesters were positively associated with placental preterm birth and spontaneous preterm birth risk, respectively (38). In our study, one third of the preterm birth cases were spontaneous, which might explain why we observed less obvious associations in the third trimester. But we did consistently observe a positive association between third trimester BPA concentrations and preterm birth risk for female infants. One cohort study in China reported that both second and third trimester urinary BPA concentrations were associated with higher preterm birth risk (37), which is also consistent with our study findings. Similarly, another nested case-control study with 30 preterm birth cases in Mexico City found that third trimester urinary BPA concentrations were higher among mothers who delivered preterm compared with concentrations in those who delivered full term; however, the results were only significant in unadjusted models and the study did not quantify BPA at first or second trimester (39). These two studies did not examine infant sex as a modifier. Additionally, other studies examined gestational age as a continuous outcome in relation to prenatal BPA exposure. Two cross-sectional studies reported lower gestational age (days) with higher urinary BPA concentrations at delivery (40, 41). In contrast, a cohort study in Puerto Rico found that urinary BPA concentrations in the early second trimester (16–20 weeks) were associated with lower odds of preterm birth and prolonged gestational age among 607 women. However, these associations were attenuated in relation to middle and late second trimester concentrations (24). Differences in demographics in this Puerto Rican cohort compared with the present study included a higher proportion of multiparous women (52% vs. 17%), a slightly higher preterm birth rate (10% vs. 8%), and a doubling of second trimester BPA concentrations (SG-corrected GM [GSD]: 2.16 [2.49] vs. 1.04 [0.06] ng/mL), respectively. In addition, the investigators did not consider maternal race, a strong indicator for preterm birth especially in the context of Puerto Rico (65) nor patterns of BPA exposure across the whole pregnancy (66), which likely contributed to these inconsistencies with our findings.

In our study, we report that first trimester paraben concentrations were positively associated with a higher risk of preterm birth. Similarly, a nested case-control study in Boston found that first and early second trimester urinary ethylparaben concentrations were associated with higher odds of placental preterm birth (46). Another cohort study in New York reported null findings between third trimester paraben concentrations and preterm birth. However, in examining gestational age continuously, the investigators found third trimester butylparaben exposure was associated with shorter gestational duration (67). In contrast, Aker et al. (24) observed mean second trimester urinary methyl- and propyl-paraben concentrations were associated with longer gestational duration in a cohort study in Puerto Rico. Of note, this cohort had lower parabens concentrations across trimesters than those of our study participants, and again the investigators did not consider race in their analyses, which may be an important confounder. No prior study examined sex differences in relation to paraben exposure and preterm birth risk. Our sex-specific findings should therefore be interpreted cautiously in light of the limited power to detect differences and the possibility of false-positive results.

We reported that urinary triclosan concentrations were negatively associated with preterm birth risk. Only two studies investigated the association between prenatal triclosan exposure and the risk of preterm birth. A nested case-control study found second trimester triclosan concentrations were associated with diminished risk of spontaneous preterm birth (46). Although a cohort study in Puerto Rico found no association between mean second trimester urinary triclosan concentrations and preterm birth, they did report shorter gestational duration among female infants and longer pregnancy length among male infants (24), which was similar to our findings. As for gestational age as the outcome, in a Chinese cohort with relatively low urinary triclosan detection frequencies, triclosan concentrations at delivery were associated with longer gestational age, although association were null in adjusted models (68). However, a prospective cohort

FIGURE 3



Relative urinary bisphenol A concentrations across gestation comparing preterm and non-preterm births, stratified by infant sex. Models were adjusted for age (continuous), body mass index (continuous), assisted reproductive technology (yes/no), smoking (ever/never), education (no college, college, graduate degree), and race or ethnicity (White, Black or African American, Asian, other).

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in the United States found the mean second trimester urinary triclosan concentration was associated with shorter gestational duration, and no sex differences were observed (8). Findings on gestational age may not reflect the associations on preterm birth.

In our study, first trimester urinary benzophenone-3 concentrations were associated with lower preterm birth risk with this potential protective effect being more evident among male compared with female infants. Aker et al. (24) observed that the second trimester bezophenone-3 concentration was negatively associated with the odds of preterm birth. This study had significantly lower urinary benzophenone-3 concentrations than those in our study (SG-corrected GM [GSD]: 39.45 [6.63] vs. 166 [20.8] ng/mL, respectively). In contrast, another study found that the urinary benzophenone-3 concentrations at delivery were associated with shorter pregnancy length in male but not female infants (40). Heterogeneous designs in sample collection might explain the differences.

Although we report potential protective associations of both triclosan and benzophenone-3, the literature evidence is overall limited and inconsistent. Caution in interpretation is also warranted given that prolonged gestation might lead to post-term pregnancy and increase the risk of stillbirth, maternal or neonatal complications, and cesarean delivery (69, 70). It is possible that protective associations may be confounded by healthy lifestyles factors during pregnancy. Benzophenone-3 is mainly used in sunscreen lotions, and thus a higher benzonphenone-3 concentration suggests more sunlight exposure and hence possibly higher vitamin D levels, thereby decreasing preterm birth risk via a potential vitamin D pathway (71–73). Similarly, higher urinary triclosan concentrations might indicate good hygiene and a lower likelihood of prenatal infections or even gingivitis. Triclosan is used as an antimicrobial in select consumer products, including toothpaste. Thus, lower preterm birth risk may occur via reducing inflammation/infection (74). Future studies will help to confirm or rule out these observed protective associations.

Despite the relatively small sample size, a potential association between prenatal BPS exposure and higher preterm birth risk cannot be excluded, given the present results. A recent nested case-control study in Boston reported that BPS detection in the late third trimester was associated with higher odds of preterm birth and no interaction with infant sex was observed (46). This study had a lower BPS detection rate than that in our study (20% vs. 70%), and it modeled the exposure as a dichotomized variable denoting detected/non-detected, which might explain the discordance. In contrast, a Chinese cohort reported no association between prenatal urinary BPS concentrations measured at any trimester and preterm birth (37). Further epidemiologic studies are needed to better understand the potential influence of prenatal BPS exposure on birth outcomes.

The biologic pathways through which environmental phenols may influence gestation length are not fully clear. However, inflammation, oxidative stress, and endocrine disruption are the main hypothesized modes of action (2). The biologic plausibility of the associations observed is particularly strong for BPA. BPA is a recognized reproductive toxicant (26) that has been shown to impair uterine receptivity and implantation (75), placentation (76, 77), and steroid levels and signaling during gestation (78) in experimental animals. Additionally, BPA may promote oxidative stress and inflammation in female reproductive organs and placental tissue as shown in laboratory studies (44, 79). BPA has also been associated with increased levels of systemic oxidative markers in pregnant women (80, 81). Increased oxidative

stress may lead to poor placentation in early pregnancy (82), and premature rupture of membranes during late pregnancy (83–87). Moreover, late pregnancy inflammation could also initiate changes leading to cervical ripening, rupture of the amniotic sac, and/or increased myometrial contractility resulting in preterm birth (65, 88). BPS and several parabens have been shown to induce oxidative stress and impair hormonal signaling in female reproductive tissues (89–91) and are linked to oxidative stress markers in pregnant women (92, 93). Although benzophenone-3 is also suspected of interfering with steroid hormone regulation (25), and triclosan may interact with the thyroid axis (30), limited experimental data exist in relation to perinatal outcomes. The observed sex differences may be because of the differences in the expression of endocrine receptors between female and male fetuses. Estrogen and progesterone receptors messenger ribonucleic acid were differentially expressed in female fetal cells (94), which might make the female fetus more susceptible to endocrine disruptors acting through estrogenic mechanisms, and this may be the case for both BPA (95) and parabens (32). Additionally, previous studies have also shown that female fetuses were more sensitive to inflammation (96, 97). Future studies should explore the underlying mechanisms of potential sex differences between environmental chemicals and preterm birth.

Notably, the previous analyses of our cohort reported that maternal preconception BPA and BPS concentrations were associated with increased preterm birth risk, suggesting the involvement of a potential epigenetic mechanism on gametes or female reproductive tissues predisposing to preterm birth (98). In the present study, we extended these results, additionally showing that sustained prenatal exposure to bisphenols may also contribute to prematurity, probably through different mechanisms depending on the specific trimester of the exposure. Indeed, sex-specific associations with preterm birth were only observed with prenatal exposures, in line with the different hormonal milieus of male and female fetuses. We found that the second trimester appeared to be the most relevant window for the influence of BPA on preterm birth. Together with previous findings in the EARTH Study showing BPA-glucose positive associations also during the second trimester (99), our results suggest that the associations between BPA and preterm birth may have resulted from a combination of both epigenetic and metabolic mechanisms in different windows. Another implication of these findings is that the inconsistencies observed in prenatal studies could be because of the frequently hidden influence of preconception exposures, which was not accounted for.

A major strength of this study was the use of two statistical methods to identify vulnerable prenatal windows and better examine the robustness and consistency of the associations. Multiple informant models generated more precise results compared with a set of separate modified Poisson regressions, and additionally enabled us to compare the associations across trimesters to assess vulnerability windows. Triangulation of the two methods showed consistent associations, which may counteract the imprecision of the study. Second, in the fertility treatment setting, gestational age was estimated with high accuracy by using IVF protocol dates, substantially reducing misclassification of preterm birth because of inaccuracies in pregnancy dating (100). In addition, the EARTH Study allowed for a timely assessment of exposure to BPA replacements such as BPS. This study also had several limitations that should be considered in light of our findings. First, despite our best effort, potential selection bias caused by missingness of any trimester data might not be fully addressed by the inverse probability weighting methods we applied. As such, caution should be taken in interpreting the results for the third trimester. Second, exposure misclassification using biomarker concentrations in spot urine samples collected throughout pregnancy cannot be ruled out because of the relatively short biologic half-lives and episodic nature of exposure to these nonpersistent chemicals. Third, this study was conducted among subfertile women who attended a fertility clinic and thus may not be directly generalizable to fertile women or those not seeking treatment. Notwithstanding, our findings are comparable in direction and magnitude to those from other prenatal cohorts (24, 37–41, 46, 67, 68). Although we sought to evaluate sex-specific differences in the outcome by infant sex in response to prenatal phenols exposure, we realize that our results showing a higher risk among female infants (BPA in second and third trimester) and early birth should be interpreted with caution given our small numbers and limited power. We were also unable to examine the subtypes of preterm birth (e.g., spontaneous vs. induced) because of the sample size. Although multiple comparisons were conducted, our interpretation of the findings was based on the degree of consistency after applying different but complementary statistical methods. Finally, the seemingly protective associations between benzophenone-3 and triclosan and preterm birth might be confounded by healthy lifestyle factors during pregnancy, and should be evaluated in future studies.

CONCLUSION

Urinary BPA concentrations were higher among those with preterm births throughout several gestation weeks compared with non-preterm births. We found some preliminary evidence of associations between mid-to-late pregnancy BPA concentrations and early pregnancy paraben concentrations with preterm birth among female infants only. Although the relationship for BPA was especially evident starting in mid-pregnancy, a unique critical window could not be identified with precision in this work. Future studies should validate the most vulnerable windows and the sex-specific associations and explore potential mechanisms. Results should also be confirmed in larger studies and in a population without fertility concerns.

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Data Availability: Data are available on request.

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Concentraciones urinarias prenatales de fenoles y riesgo de parto prematuro: explorando ventanas de vulnerabilidad.

Objetivo: Explorar ventanas ~~o intervalos~~ de vulnerabilidad a concentraciones de fenol en orina prenatal y ~~al~~ su asociación con parto prematuro.

Diseño: Cohorte prospectiva.

Entorno: Gran centro de fertilidad en Boston, Massachusetts.

Paciente (s): Un total de 386 madres que buscaron tratamiento de fertilidad y dieron a luz a un hijo único entre 2005 y 2018.

Intervención (es): Ninguna.

Medida (s) de resultado principal: Nacidos vivos únicos con edad gestacional <37 semanas completas.

Resultado (s): En comparación con las mujeres con partos no prematuros, las concentraciones urinarias de Bisfenol A (BPA) fueron más altas durante las gestaciones de mujeres con partos prematuros, particularmente durante el periodo medio o tardío del embarazo y entre las que ya tienen bebés. Las concentraciones de BPA en el segundo trimestre se asociaron con el parto prematuro (índice de riesgo [RR] 1,24; IC del 95%: 0,92, 1,69), que se llevó a cabo principalmente en bebés femeninos (RR 1,40; IC del 95%: 1,04; 1,89) y no en varones (RR 0,85; IC del 95%: 0,50; 1,46). Las concentraciones de parabenos durante el primer trimestre también se asociaron con el parto prematuro (RR 1,17; IC del 95%: 0,94, 1,46) y, de manera similar, la asociación solo se observó
para los bebés femeninos (RR 1,46; IC del 95%: 1,10; 1,94) y no en varones (RR 0,94; IC del 95%: 0,72; 1,23).
Las concentraciones de Bisfenol S en orina del primer trimestre mostraron un posible riesgo de parto prematuro (RR 1,25; IC del 95%: 0,82, 1,89), aunque el pequeño número de casos impidió un examen específico por sexo.

Conclusión (es): Encontramos evidencia preliminar de asociaciones entre las concentraciones de BPA en el embarazo medio y tardío, y de parabeno al comienzo del embarazo con parto prematuro entre aquellos con bebés femeninos solamente. El riesgo de parto prematuro puede ser compuesto, por sexo y ventana específico. Dado el limitado tamaño de la muestra de esta cohorte, los resultados deben confirmarse en estudios más amplios, incluidas en las poblaciones fértiles.