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Maternal and paternal preconception exposure to phenols and preterm birth

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ABSTRACT

Background: Phenol exposure during pregnancy has been associated with preterm birth, but the potential effect of preconception exposure in either parent is unknown. There is a growing body of evidence to suggest that the preconception period is a critical window of vulnerability for adverse pregnancy outcomes.
Objective: We examined whether maternal and paternal preconception urinary concentrations of select phenols were associated with the risk of preterm birth among couples attending fertility care.
Methods: The analysis included 417 female and 229 male participants of the Environment and Reproductive Health (EARTH) Study who gave birth to 418 singleton infants between 2005 and 2018 and for whom we had phenol biomarkers quantified in at least one urine sample collected before conception. Mothers and fathers provided an average of 4 and 3 urine samples during the preconception period, respectively. We calculated the geometric mean of bisphenol A (BPA), bisphenol S (BPS), benzophenone-3, triclosan, and the molar sum of parabens (ΣParabens) urinary concentrations to estimate each participant's preconception exposure. Risk ratios (RRs) of preterm birth (live birth before 37 completed weeks' gestation) were estimated using modified Poisson regression models adjusted for covariates.
Results: The mean (SD) gestational age among singletons was 39.3 (1.7) weeks with 8% born preterm. A natural log-unit increase in maternal preconception BPA (RR 1.94; 95% CI: 1.20, 3.14) and BPS (RR 2.42; 95% CI: 1.01, 5.77) concentration was associated with an increased risk of preterm birth. These associations remained after further adjustment for maternal prenatal and paternal preconception biomarker concentrations. Paternal preconception ΣParabens concentrations showed a possible elevated risk of preterm birth (RR 1.36; 95% CI: 0.94, 1.96). No consistent pattern of association was observed for benzophenone-3 or triclosan biomarkers in either parent.
Discussion: Maternal preconception urinary BPA and BPS concentrations, as well as paternal preconception urinary parabens concentrations were prospectively associated with a higher risk of preterm birth. Subfertile couples' exposure to select phenols during the preconception period may be an unrecognized risk factor for adverse pregnancy outcomes.

1. Introduction

Preterm birth is a leading cause of perinatal and infant morbidity worldwide (Romero et al., 2014; Rubens et al., 2014) and is a relatively common perinatal outcome with around one in ten babies born with this condition in Europe and in the United States (U.S.)

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(Chawanpaiboon et al., 2019; EFCNI, 2010; WHO, 2012). Prenatal exposure to endocrine disrupting chemicals (EDCs) is considered a potential risk factor for preterm birth (Ferguson and Chin, 2017; Porpora et al., 2019). EDCs are exogenous chemicals that can interfere with any aspect of hormone action (Zoeller et al., 2012). Phenolic EDCs are of particular concern, as human exposure is ubiquitous and occurs through diet, use of personal care products, and multiple other lifestyle-related sources (Frederiksen et al., 2014; Freire et al., 2019; Messerlian et al., 2017).

Bisphenol A (BPA) is a paradigmatic EDC that disrupts hormonal homeostasis at low doses in experimental studies (Vandenberg et al., 2012), and is classified as an ovarian and reproductive toxicant (ECHA, 2016; Peretz et al., 2014). Despite this, BPA is extensively used in the manufacturing of polycarbonate plastics, epoxy resins liners of canned food, and thermal paper, among numerous other applications (Mustieles et al., 2015; Vandenberg et al., 2007; von Goetz et al., 2017). Increasing public concern over BPA has led to its replacement in some consumer products often labeled as "BPA-free." However, most replacements are structural analogs such as bisphenol S (BPS), which are also hormonally active (Rochester and Bolden, 2015) and are suspected of having similar adverse effects in experimental animals (Carvaillo et al., 2019). BPA to BPS replacement is a concern in many countries (Kataria et al., 2017; Molina-Molina et al., 2019; Ye et al., 2015), with the speed of substitution being relatively faster in the United States market compared to other countries (Wu et al., 2018). Other phenolic EDCs such as parabens and triclosan are frequently used in personal care products, food additives, and pharmaceuticals to prevent microbial growth (Ferguson et al., 2017; Giulivo et al., 2016), while benzophenone-3 is used as an ultraviolet filter in sunscreens, body lotions, and make-up, among other uses (Liao and Kannan, 2014). Despite concern about the potential endocrine action of these phenols (Ghazipura et al., 2017; Johnson et al., 2016; Nowak et al., 2018), epidemiologic evidence on birth outcomes is limited (Giulivo et al., 2016; Jamal et al., 2019; Messerlian et al., 2018a).

New and emerging data highlights the potential for EDCs to exert enduring epigenetic modifications in male and female gametes, as well as in other female reproductive organs (Luderer et al., 2019; Santangeli et al., 2017; Xin et al., 2015; Zama and Uzumcu, 2010). Further, epigenetic modifications likely contribute to preterm birth etiology (Mani et al., 2018; Menon et al., 2012) and have been recently identified as a key characteristic of female reproductive toxicants (Luderer et al., 2019). The preconception period is thus increasingly recognized as a highly sensitive window for environmental perturbation, via both maternal and paternal exposures (Braun et al., 2017; Toivonen et al., 2017). However, while some epidemiologic studies have previously explored the relationship between prenatal exposure to phenols and the risk of delivering preterm (Aung et al., 2019; Behnia et al., 2016; Cantonwine et al., 2010, 2015; Huo et al., 2018), the impact of preconception EDC exposures on preterm birth constitutes a knowledge gap (Toivonen et al., 2017). Therefore, our objective was to examine whether maternal and paternal urinary phenol biomarker concentrations measured before conception were associated with preterm birth in a prospective preconception cohort of couples attending a fertility clinic.

2. Methods

2.1. Study cohort

The Environment and Reproductive Health (EARTH) Study is an ongoing prospective preconception cohort of couples from the Massachusetts General Hospital (MGH) Fertility Center. The EARTH Study aims to investigate how environmental and nutritional factors in both males and females from preconception throughout pregnancy influence fertility, gestation, and birth outcomes. The cohort has been previously described in detail (Messerlian et al., 2018b). Briefly, women 18–46 and men 18–55 years of age are invited to enroll independently or as a couple, and are followed from study entry throughout their fertility care, pregnancy, and labor and delivery. Participants complete general and lifestyle questionnaires, undergo anthropometric measurements, and provide a spot urine and blood sample at baseline and then subsequently during each fertility treatment cycle, as well as across trimesters among those females achieving pregnancy.

The present study included 417 female and 229 male EARTH cohort participants who gave birth to a singleton infant between 2005 and 2018 and for whom we quantified phenol biomarkers in at least one urine sample collected before conception of the index pregnancy. One male participant enrolled without a female partner and had a singleton live birth, thus leaving 228 couples. Among the 418 singleton infants, preconception BPA measurements were available for 417 mother–child pairs and 229 father-child pairs, and paraben concentrations were available for 405 mother–child and 223 father-child pairs. Measurement of benzophenone-3 and triclosan began in 2010; preconception urinary concentrations were available for 278 mother–child pairs and 139 father-child pairs. Measurement of BPS did not begin until 2012; urinary concentrations were available for 163 mother–child pairs and 77 father–child pairs (See Fig. 1, Participant Flow Chart). Trained study staff explained the study details to all participants and answered any questions before obtaining their signed informed consent. The study was approved by the Institutional Review Boards of MGH, Harvard T.H. Chan School of Public Health, and the Centers for Disease Control and Prevention (CDC).

2.2. Exposure assessment

Male and female participants provided one spot urine sample at study entry. Females provided up to two additional spot urine samples per fertility treatment cycle: the first sample collected during the follicular phase of the cycle (days 3 to 9) and the second obtained on the day of the fertility procedure [at time of oocyte retrieval, or embryo transfer for fresh or frozen in-vitro fertilization (IVF) treatment, or on the day of intrauterine insemination (IUI)]. During pregnancy, women also provided one spot urine sample per trimester at median 6, 21, and 35 weeks' gestation. Males provided an additional spot urine sample per cycle on the day when their female partner underwent the fertility procedure. We used multiple urine samples per participant obtained from study entry up to and including the samples from the cycle of conception of the index pregnancy to estimate mean exposure in the preconception window.

Urine was collected in a polypropylene specimen cup and analyzed for specific gravity (SG) with a handheld refractometer (National Instrument Company, Inc., Baltimore, MD, USA), divided into aliquots, and frozen for long-term storage at −80 °C. All samples were shipped on dry ice overnight to the CDC (Atlanta, GA, USA) for quantification of urinary phenol concentrations using solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry (Zhou et al., 2014). The urinary concentrations of the following phenols were measured: BPA, BPS, methylparaben, ethylparaben, propylparaben, butylparaben, benzophenone-3 and triclosan. The limits of detection (LOD) ranged from 0.1 to 1.0 ng/ml. Concentrations below the LOD were assigned the LOD divided by the square root of two (Hornung, 1990). Due to low detection frequencies and small number of participants with ethylparaben quantified, we did not include or consider ethylparaben in further analyses. The weighted molar sum of parabens was calculated by dividing each urinary concentration by its molecular weight and then summing: $\Sigma Parabens = [(Methylparaben * (1/152.15\ g/mol)) + (Propylparaben * (1/180.20\ g/mol)) + (Butylparaben * (1/194.23\ g/mol))]$. We then weighted this sum by the molecular weight of methylparaben (152.15 g/mol) to convert the molar concentration to units of ng/mL.

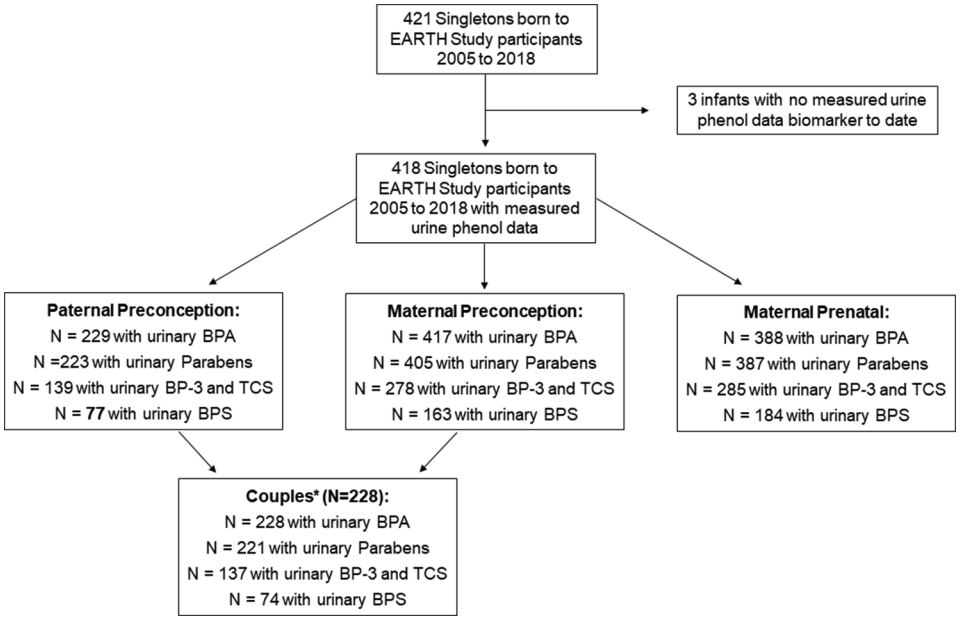

Fig. 1. Participant flow-chart and phenol biomarker data available in the EARTH Study 2005–2018. Abbreviations: bisphenol A (BPA); bisphenol S (BPS); benzophenone 3 (BP-3); triclosan (TCS). * Note: One male participant joined without female partner, leaving 228 couples.

2.3. Outcome assessment

Gestational age in days was abstracted from delivery records and validated using the American College of Obstetricians and Gynecologists (ACOG) guidelines to estimate gestational age for births following medically assisted reproduction (ACOG, 2014). The fertility treatment setting permitted us to estimate gestational age with high accuracy using *in vitro* fertilization (IVF) embryo transfer dates, substantially reducing misclassification of preterm birth due to inaccuracies in pregnancy dating (Savitz et al., 2002). For IVF pregnancies, gestational age was estimated as (outcome date – embryo transfer date + 14 days + cycle day of transfer) (ACOG, 2014). For IUI and non-medically assisted/naturally conceived pregnancies, we used birth date minus cycle start date. Gestational age was corrected if medical delivery record estimates (gold standard) differed by over 6 days from the estimated gestational age using the described methods (corrected for three infants through additional chart verification). Preterm birth was defined as any live birth prior to 37 weeks of completed gestation (< 259 days).

2.4. Covariates

At study entry, paternal and maternal age, education, race, and smoking status were obtained from self-reported questionnaires. A research study staff measured the height and weight of participants, and Body Mass Index (BMI) (kg/m^2) was calculated. The physician administering fertility treatment diagnosed any underlying cause of infertility using the Society for Assisted Reproductive Technology (ART) definitions. Type of medically assisted reproduction used in the conception cycle of the index birth was abstracted from the electronic medical records by trained study staff and dichotomized: ART procedures (e.g., stimulated IVF cycles with fresh embryo transfers or cryo-thawed embryo transfer protocols) versus non-ART protocols (e.g., IUI with or without ovulation induction/stimulation; ovulation induction/stimulation with timed intercourse, or non-medically assisted/naturally conceived).

2.5. Statistical analysis

To account for urinary dilution, we adjusted concentrations by multiplying each biomarker concentration by [(SG_p-1)/(SG_i-1)], where SG_i is the SG of the participant's urine sample and SG_p is the mean SG for all male (mean = 1.016) or all female (mean = 1.015) participants included in the study samples (Pearson et al., 2009). The SG-adjusted biomarker concentrations were natural log-transformed to standardize the distribution and reduce the influence of extreme values. We estimated geometric mean paternal and maternal preconception phenol biomarker concentrations by averaging each participant's log concentration obtained from all urine samples collected from study entry and at each treatment cycle up to and including the cycle of the index conception of the singleton.

We calculated descriptive statistics for biomarker concentrations using SG-adjusted log concentrations, percentage of values below the LOD, as well as Spearman correlation coefficients for log concentrations between couples (paternal versus maternal preconception and across preconception and prenatal windows). We described the clinical and demographic characteristics of the study population with means (standard deviation (SD)) or proportions (n, %). We fit modified Poisson regression models to evaluate the association of continuous urinary biomarker concentrations and dichotomous preterm birth outcomes. Models were fit using a log link function and Poisson distribution to yield estimated risk ratios (RRs) and 95% confidence intervals (CIs) for preterm birth for every natural log-unit increase in biomarker concentration. We fit a separate model for each individual phenol biomarker.

We selected *a priori* covariates as potential confounders based on substantive knowledge using a directed acyclic graph (DAG, see Fig. 2) (Textor et al., 2016) and examined unadjusted and covariate-adjusted models. Models evaluating maternal preconception exposure were adjusted for: maternal age and BMI (continuous), maternal education (< college, college, graduate degree), smoking status (never smoked versus ever smoked, defined as a current or former smoker), and ART vs. non-ART-based treatment. Both paternal and maternal covariates in reproductive epidemiologic studies are increasingly considered in confounding models (Bellavia et al., 2019). The study of paternal preconception exposure is still a novel field; we thus chose to be more conservative in models of father's exposure. Paternal models were therefore adjusted for both the maternal covariates presented in our DAG in Fig. 2, as well as for father's age (continuous), BMI (continuous), and smoking (never *vs.* ever). We also adjusted for partner's

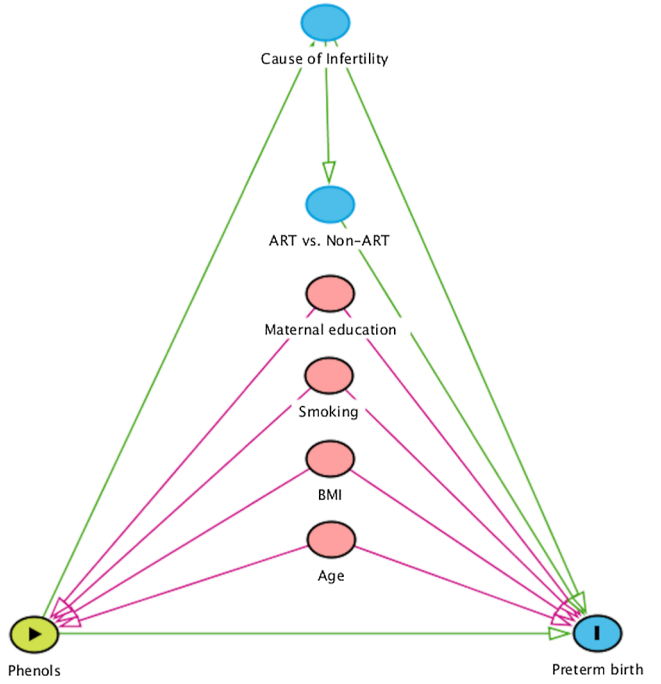

Fig. 2. Hypothesized directed acyclic graph (DAG) between preconception exposure to phenols and preterm birth risk. Abbreviations: body mass index (BMI); assisted reproductive technology (ART).

preconception exposure in subsequent models. To account for potential confounding by pregnancy-related exposure, we adjusted for mean prenatal log-concentrations across three trimesters for the biomarker of interest in additional multivariable models. Statistical analyses were conducted with SAS (version 9.4; SAS Institute Inc., Cary, USA).

2.6. Sensitivity analyses

To explore potential dose–response associations within positive findings, we created and fit models across biomarker quartiles. Given that the placenta shows sex-dependent functions susceptible to environmental insults (Rosenfeld, 2015), and previous sex-specific associations have been reported between prenatal phenol exposure and preterm birth (Aker et al., 2019; Cantonwine et al., 2015), we stratified analyses by infant sex and estimated sex-specific risk ratios and 95% CIs (Buckley et al., 2017). We calculated effect-measure modification p-values for the interaction term (sex × urine phenol biomarker concentration) and considered < 0.20 as potential evidence of effect modification by infant sex on the multiplicative scale. In a previous study, we found a downward trend in preconception BPA concentrations among EARTH participants starting in 2012 up to 2018 (Mínguez-Alarcón et al., 2019). As such, we chose to further adjust for study period ($\leq$2011 *vs.* $\geq$ 2012) in our maternal and paternal preconception BPA models. Furthermore, because the number of completed fertility cycles may influence both the number of urine samples collected for estimating exposure as well as adverse birth outcomes, we included a sensitivity analysis additionally adjusting for the number of fertility cycles in order to test the robustness of the main findings.

3. Results

3.1. Study cohort

Our cohort included 417 mothers and 229 fathers (228 couples) with an average age of 34.7 and 36.0 years and a mean BMI of 24.1 and 27.7 at recruitment, respectively (Table 1). Among the 418 singleton infants, mean gestational age was 39.3 (SD = 1.7) weeks, with 8.1% (n = 34) of infants born preterm (Table 2). Mean birth weight was 3360 (SD = 550) grams, with 4.8% (n = 20) of infants born low birth weight (< 2500 g) (Table 2).

Table 1
Parental characteristics from 417 women and 229 men participating in the Environment and Reproductive Health (EARTH) Study (2005–2018).

Parental Characteristic	Mothers	Fathers
	N = 417	N = 229
Age (years)		
Mean ± SD	34.7 ± 4.0	36.0 ± 4.6
Age > 35, n (%)	172 (41)	127 (55)
Race, n (%)		
White	353 (85)	201 (88)
Black	11 (3)	4 (2)
Asian	36 (8)	15 (6)
Other	17 (4)	9 (4)
Body Mass Index (BMI, Kg/m^2)		
Mean ± SD	24.1 ± 4.3	27.7 ± 6.1
BMI > 25, n (%)	132 (32)	156 (68)
Education, n (%)		
< College	54 (13)	31 (17)
College Graduate	135 (32)	62 (34)
Graduate Degree	228 (55)	87 (49)
Smoking Status, n (%)		
Never	314 (75)	159 (69)
Ever (former or current)	103 (25)	70 (31)
Infertility Diagnosis, n (%)		
Male Factor	100 (24)	69 (30)
Female Factor	132 (32)	65 (28)
Unexplained	185 (44)	95 (42)
Primiparous, n (%)	346 (83)	–

Table 2
Birth characteristics of 418 singletons from the Environment and Reproductive Health (EARTH) Study (2005–2018).

Child Characteristics	Births 2005–2018
	N = 418
Male, n (%)	216 (52)
Birth weight (grams)	
Mean ± SD	3360 ± 550
min–max	1090–5040
Low birth weight	
< 2500 g, n (%)	20 (4.8)
Gestational age at birth	
Mean weeks ± SD	39.3 ± 1.7
min–max	29–42
Mean days ± SD	275 ± 12.0
min–max	205–294
Preterm birth	
< 37 weeks, n (%)	34 (8.1)
Mode of conception, n (%)	
ART [a]	236 (56)
Non-ART [b]	182 (44)

[a] Assisted Reproductive Technology (ART): fresh or frozen in-vitro fertilization protocols, including intracytoplasmic sperm injection.
[b] Non-ART: intrauterine insemination with or without ovulation induction/stimulation; ovulation induction/stimulation with timed intercourse, or non-medically assisted/naturally conceived.

3.2. Urinary phenol concentrations

In total, 1693 maternal preconception and 547 paternal preconception urine samples were quantified for phenol biomarkers. Women and men provided on average 4.0 (range: 1–20) and 2.6 (range: 1–10) urine samples, respectively. Table S1 presents the distribution of SG normalized mean urinary phenol biomarker concentrations. Within the measured phenols, the geometric mean of the SG-adjusted urinary concentrations for fathers and mothers were respectively: 1.4 and 1.1 ng/ml for BPA; 0.48 and 0.48 ng/ml for BPS; 30.7 and 142.9 ng/ml

for ΣParabens; 63.4 and 161 ng/ml for benzophenone-3; and 14.6 ng/ml and 14.0 ng/ml for triclosan (Table S1). The frequency of detection was lowest for paternal preconception butylparaben (25.8%). The remaining paternal and maternal preconception phenol concentrations had moderate to high detection frequencies ranging from 63.2% to 99.7% (Table S1). The lowest Spearman correlation coefficients were observed for maternal and paternal preconception BPS concentrations (r = 0.09) and maternal preconception and prenatal BPS concentrations (r = 0.15). Other biomarkers presented moderate correlations for maternal and paternal preconception concentrations (r = 0.23–0.59) and maternal preconception and prenatal concentrations (r = 0.27–0.60) (Table S2).

3.3. Maternal preconception window

Covariate-adjusted models showed a positive association between maternal preconception urinary BPA concentrations and the risk of preterm birth (RR 1.94; 95% CI: 1.20, 3.14). This association was strengthened slightly in models additionally adjusted for maternal prenatal BPA concentrations (RR 2.20; 95% CI: 1.29, 3.75), and remained in models further adjusted for paternal BPA concentrations (RR 2.00; 95% CI: 1.00, 3.99) (Table 3). Sensitivity analyses revealed a linear trend across quartiles of maternal preconception BPA concentrations and preterm birth risk (P test for trend = 0.01) (Table S3). No significant difference was observed between male and female infants in the association of maternal preconception BPA concentration and preterm birth (P value for sex interaction term = 0.32) (Table S5). Further adjustment for study period and number of fertility cycles did not materially change the association between maternal preconception BPA concentrations and preterm birth (RR 1.76; 95% CI: 1.02, 3.02) (Table S6).

We also observed that higher maternal preconception urinary BPS concentrations were associated with an elevated risk of preterm birth in the covariate-adjusted model (RR 2.42; 95% CI: 1.01, 5.77), with a similar pattern of strengthened associations after further adjustment for maternal prenatal BPS concentrations (RR 3.33; 95% CI: 1.13, 8.80) (Table 3). No differences by infant sex were observed with BPS (P value for sex interaction term = 0.68) (Table S5). The positive association between maternal preconception BPS and preterm birth remained after adjusting for number of fertility cycles (RR 2.61; 95% CI: 1.03, 6.57) (Table S6). Although mothers with higher preconception urinary triclosan concentrations had lower preterm birth risk (RR 0.78; 95% CI: 0.59, 1.04), confidence intervals became more imprecise after controlling for prenatal triclosan (RR 0.78; 95% CI: 0.53, 1.14) (Table 3). No consistent pattern of association compatible with the data was observed for maternal preconception ΣParabens or benzophenone-3 concentrations (Table 3). In sex-stratified analyses, maternal preconception ΣParabens concentrations were associated with preterm birth among female but not male infants (P value for sex interaction term = 0.13, Table S5).

3.4. Paternal preconception window

No association with preterm birth was observed for paternal preconception urinary BPA concentrations (RR 0.82; 95% CI: 0.43, 1.55), BPS (RR 0.49; 95% CI: 0.08, 2.98), benzophenone-3 (RR 1.02; 95% CI: 0.53, 1.99) or triclosan (RR 0.97; 95% CI: 0.67, 1.41) (Table 4). Fathers with higher urinary concentrations of ΣParabens had singletons with a higher but imprecise risk of preterm birth in the main covariate-adjusted model (RR 1.36; 95% CI: 0.94, 1.96). This was unchanged with further adjustment for maternal preconception (RR 1.42; 95% CI: 0.97, 2.09) or pregnancy ΣParabens concentrations (RR 1.39; 95% CI: 0.95, 2.04) (Table 4). Further adjustment for number of fertility cycles did

Table 3
Risk Ratios (RR) and 95% Confidence Intervals (95% Cis) for preterm birth (< 37 weeks) per natural log-unit increase in maternal preconception urinary phenol concentrations among 417 mothers in the Environment and Reproductive Health (EARTH) Study, 2005–2018.

Phenol Biomarker	Preterm Birth Model 1 Unadjusted[a]	Preterm Birth Model 2 Covariates[b]	Preterm Birth Model 3 Covariates + Prenatal[c]	Preterm Birth Model 4 Covariates + Paternal Precon[d]
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Bisphenol A				
	1.95 (1.23, 3.09)	1.94 (1.20, 3.14)	2.20 (1.29, 3.75)	2.00 (1.00, 3.99)
p-values	0.005	0.007	0.004	0.05
Preterm Birth n/N	34/417	34/417	31/384	18/228
Bisphenol S				
	2.31 (1.04, 5.14)	2.42 (1.01, 5.77)	3.33 (1.13, 8.80)	DNC
p-values	0.04	0.05	0.03	
Preterm Birth n/N	9/163	9/163	7/145	2/74
ΣParabens[e]				
	0.99 (0.76, 1.29)	0.99 (0.76, 1.30)	0.90 (0.63, 1.29)	1.00 (0.65, 1.54)
p-values	0.93	0.95	0.57	0.99
Preterm Birth n/N	33/405	33/405	30/372	17/221
Benzophenone-3				
	0.91 (0.70, 1.19)	0.91 (0.68, 1.22)	0.93 (0.63, 1.39)	1.55 (0.89, 2.70)
p-values	0.50	0.53	0.74	0.12
Preterm Birth n/N	21/278	21/278	18/254	8/137
Triclosan				
	0.77 (0.58, 1.02)	0.78 (0.59, 1.04)	0.78 (0.53, 1.14)	1.16 (0.68, 1.97)
p-values	0.07	0.10	0.19	0.59
Preterm Birth n/N	21/278	21/278	18/254	8/137

Note: n, number of preterm birth cases; N, sample size for maternal preconception biomarker concentrations; DNC, did not converge.

[a] Models 1: Unadjusted.

[b] Models 2: Adjusted for age (continuous), BMI (continuous), ART (yes/no), smoking (ever/never), education (categorical).

[c] Models 3: Adjusted for age (continuous), BMI (continuous), ART (yes/no), smoking (ever/never), education (categorical) + prenatal biomarker exposure (continuous log-concentration).

[d] Models 4: Adjusted for age (continuous), BMI (continuous), ART (yes/no), smoking (ever/never), education (categorical) + paternal preconception biomarker exposure (continuous log-concentration).

[e] ΣParabens: the molar sum of parabens was estimated by dividing each concentration by its molecular weight and then summing: ΣParabens = [(Methylparaben * (1/152.15)) + Propylparaben * (1/180.20)) + Butylparaben * (1/194.23))]. We then weighted this sum by the molecular weight of methylparaben (152.15) to convert the molar concentration to units of ng/ml.

Table 4
Risk Ratios (RR) and 95% Confidence Intervals (95% Cis) for preterm birth (< 37 weeks) per natural log-unit increase in paternal preconception urinary phenol concentrations among 229 fathers in the Environment and Reproductive Health (EARTH) Study, 2005–2018.

Phenol Biomarker	Preterm Birth Model 1 Unadjusted [a]	Preterm Birth Model 2 Covariates [b]	Preterm Birth Model 3 Covariates + Prenatal [c]	Preterm Birth Model 4 Covariates + Maternal Precon [d]
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Bisphenol A				
	0.95 (0.52, 1.74)	0.82 (0.43, 1.55)	0.82 (0.41, 1.65)	0.69 (0.35, 1.37)
p-values	0.86	0.54	0.58	0.29
Preterm Birth n/N	18/229	18/229	17/213	18/228
Bisphenol S				
	0.49 (0.08, 2.98)	DNC	DNC	DNC
p-values	0.44			
Preterm Birth n/N	2/77	2/77	1/68	2/74
ΣParabens[e]				
	1.27 (0.90, 1.77)	1.36 (0.94, 1.96)	1.39 (0.95, 2.04)	1.42 (0.97, 2.09)
p-values	0.17	0.10	0.09	0.07
Preterm Birth n/N	18/223	18/223	17/207	17/221
Benzophenone-3				
	1.01 (0.58, 1.73)	1.02 (0.53, 1.99)	0.92 (0.44, 1.94)	0.81 (0.39, 1.69)
p-values	0.98	0.95	0.83	0.58
Preterm Birth n/N	8/139	8/139	7/128	8/137
Triclosan				
	0.98 (0.67, 1.42)	0.97 (0.67, 1.41)	1.07 (0.59, 1.93)	0.86 (0.51, 1.46)
p-values	0.90	0.88	0.82	0.58
Preterm Birth n/N	8/139	8/139	7/128	8/137

Note: n, number of preterm birth cases; N, sample size for paternal preconception biomarker concentrations; DNC, did not converge; Precon, maternal preconception.
[a] Models 1: Unadjusted.
[b] Models 2: Adjusted for maternal and paternal age (continuous), maternal and paternal BMI (continuous), ART (yes/no), maternal and paternal smoking (ever/never), education (categorical).
[c] Models 3: Adjusted for maternal and paternal age (continuous), maternal and paternal BMI (continuous), ART (yes/no), maternal and paternal smoking (ever/never), education (categorical) + prenatal biomarker exposure (continuous log-concentration).
[d] Models 4: Adjusted for maternal and paternal age (continuous), maternal and paternal BMI (continuous), ART (yes/no), maternal and paternal smoking (ever/never), education (categorical) + maternal preconception biomarker exposure (continuous log-concentration).
[e] ΣParabens: the molar sum of parabens was estimated by dividing each concentration by its molecular weight and then summing: ΣParabens = [(Methylparaben * (1/152.15)) + (Propylparaben * (1/180.20)) + (Butylparaben * (1/194.23))]. We then weighted this sum by the molecular weight of methylparaben (152.15) to convert the molar concentration to units of ng/ml.

not materially change the association (RR 1.34; 95% CI: 0.93,1.93) (Table S7). An examination of the individual parabens revealed that higher paternal preconception concentrations of methylparaben (RR 1.35; 95% CI: 0.93, 1.98) and propylparaben (RR 1.27; 95% CI: 0.98, 1.65) were associated with a higher risk of preterm birth in covariate-adjusted models (Table S4). The associations between paternal preconception ΣParabens, methylparaben or propylparaben concentrations and preterm birth did not differ by infant sex (Table S5).

4. Discussion

In this prospective study of couples seeking fertility care, maternal – but not paternal – preconception BPA and BPS concentrations were both associated with an elevated risk of singleton preterm birth. These associations remained relatively unchanged after accounting for maternal prenatal or paternal preconception urinary BPA or BPS concentrations, suggesting that the maternal preconception period may be a sensitive but underexplored critical window of exposure to bisphenols. Although imprecise, paternal urinary paraben concentrations were also associated with an increased risk of early birth. We observed few differences by infant sex, however, small sample sizes within strata may have precluded our ability to detect sex-specific associations. To our knowledge, this is the first work that has assessed couples' preconception exposure to select phenols in relation to preterm birth.

Two previous maternal prenatal case-control studies have been conducted in the United States; one reporting that third trimester urinary BPA concentrations were positively associated with spontaneous preterm birth, but not all types of preterm birth (Cantonwine et al., 2015), and the other reporting higher maternal plasma BPA concentrations in mothers delivering preterm compared to women in term labor (Behnia et al., 2016). Additionally, a recent analysis in the same population studied by Cantonwine et al. (2015) observed an increased risk of spontaneous preterm delivery in relation to higher maternal urinary BPS concentrations measured during late pregnancy (Aung et al., 2019). In contrast, a study among Chinese pregnant women who provided a spot urine sample immediately after being admitted into hospital for delivery reported inverse associations between urinary BPS concentrations and pregnancy duration (Wan et al., 2018). Nevertheless, the limitations of the study by Wan et al. (2018), including the possibility of reverse causation due to the timing of urine collection, should be considered. Although our maternal preconception BPA and BPS findings could be compatible with the abovementioned studies, differences between the preconception and prenatal windows preclude additional comparisons.

In the present study, maternal preconception exposure to bisphenols appeared to influence the risk of preterm birth. Although mechanistic data on preconception environmental exposures is markedly scarce, this latent effect is compatible with the known ability of BPA to alter the epigenetic programming of the ovary and other reproductive tissues including the uterus and placenta (Santangeli et al., 2017; Suvorov and Waxman, 2015; Ye et al., 2019). Indeed, BPA was recently highlighted as an example of a female reproductive toxicant that may act through epigenetic mechanisms (Luderer et al., 2019). In support of our novel maternal preconception BPS-preterm birth association, a recent *in vivo* study has shown that BPS can also exert epigenetic modifications in oocytes at very low doses, resulting in altered female reproductive outcomes such as decreased fertilization rates (Nevoral et al., 2018). Additionally, two murine-model studies support the existence of transgenerational female reproductive effects in response to low-dose BPS exposure during gestation (Shi et al., 2019b, 2019a). Our results

are consistent with the increasing evidence that suggests similar or even stronger reprotoxic effects of BPS compared to BPA (Campen et al., 2018; Trasande, 2017; Žalmanová et al., 2017).

We previously observed that maternal preconception urinary BPA concentrations were inversely associated with offspring birth size in this same cohort (Mustieles et al., 2018). Our hypothesis of an early potential effect in the ovary, affecting oocyte quality and later resulting in reduced embryo viability and development and/or altered placental function leading to impaired fetal growth (Mustieles et al., 2018) is further supported by these preterm birth data. Importantly, such adverse pregnancy processes are also converging risk factors for preterm birth (Delnord and Zeitlin, 2019), which could have its roots in the early pre- and peri-conception period.

Although we observed that paternal paraben concentrations were associated with preterm birth, no previous epidemiologic reports with which to compare our results are available. However, in support of a potential association, parabens have been reported to increase oxidative stress in human spermatozoa (Samarasinghe et al., 2018), and butylparaben altered sperm DNA methylation in rats (Park et al., 2012). Some epidemiologic studies have reported associations between paraben exposure and altered semen quality (Zamkowska et al., 2018), while research from our own group in a smaller subsample of men did not (Meeker et al., 2011). Mechanistic studies evaluating the potential ability of parabens to exert heritable epigenetic modifications in spermatozoa could shed light on this field of study. Additional epidemiologic studies are needed to confirm or rule out the observed paternal associations with methyl- and propylparaben.

The absence of consistent preconception associations with benzophenone-3 and triclosan in our study may be compatible with previous mother–child cohorts assessing exposure during pregnancy, with most studies reporting inconsistencies. For example, null associations between prenatal urinary benzophenone-3 concentrations and preterm birth were observed among North-American women, while finding a protective association in response to higher urinary triclosan concentrations (Aung et al., 2019). Another study in Chinese pregnant women who provided a spot urine sample upon hospital admission for delivery found that benzophenone-3 concentrations were negatively associated with gestational age (Tang et al., 2013). In contrast, Aker et al. (2019) reported positive associations between maternal prenatal urinary benzophenone-3 concentrations and gestational age among Puerto Rican women, while triclosan concentrations were positively associated with gestational age in males, but negatively associated in females (Aker et al., 2019). Finally, Huo et al. (2018) did not observe associations of prenatal urinary triclosan concentrations and preterm birth risk among Chinese mothers (Huo et al., 2018). The considerable heterogeneity in these findings may be due to differences in exposure definition and measurement (e.g., gestational age at time of prenatal urine sample collection), variations in study populations, the evaluation *vs.* lack of evaluation of sex-dependent associations, or other differences in methods.

A strength of this study was the opportunity to assess both maternal and paternal exposure prior to conception, accounting for relevant potential confounders (Bellavia et al., 2019). Indeed, to our knowledge, this is the first work to examine phenol exposure in the preconception period in relation to the risk of preterm birth. Our findings may not be directly generalizable to fertile couples since subfertile mothers and fathers could be more susceptible to environmental insults. Notwithstanding, our results are consistent with previous studies reporting BPA-related adverse pregnancy outcomes in both subfertile and non-subfertile preconception cohorts (Mustieles et al., 2018; Smarr et al., 2015). Another strength is the ongoing follow-up of the EARTH Study, which allowed for a timely assessment of exposure to new chemical replacements such as BPS. BPS is suspected of causing similar reprotoxic effects as BPA, but has not undergone an exhaustive toxicological examination before its use in consumer goods (Trasande, 2017). Additionally, the assessment of diverse phenolic EDCs using multiple repeated urine samples allowed for improved exposure assessment thereby reducing exposure misclassification and its expected attenuation bias (Perrier et al., 2016). Nevertheless, some degree of exposure misclassification cannot be ruled out considering the short biological half-lives and episodic nature of exposure to these non-persistent chemicals. While a limitation was the modest number of preterm birth cases, which precluded us from studying preterm birth subtypes (i.e., spontaneous preterm labor, preterm premature rupture of membranes, placental abruption, etc.), this is one of the few studies in the field that has examined preterm birth risk under a prospective preconception cohort design. As we were not powered for estimating effect modification, small sample size within strata may have limited our ability to detect differences by infant sex. Future analyses with a higher number of male participants are warranted to confirm the reported associations with paternal preconception paraben exposure.

5. Conclusion

Maternal preconception urinary BPA and BPS concentrations as well as paternal preconception urinary paraben concentrations were prospectively associated with an increased risk of preterm birth. Our results suggest that couples' exposure to select phenols during preconception, especially exposure to bisphenols, is an overlooked risk factor for adverse pregnancy outcomes. These findings may have significant public health implications given the importance of the outcome, the ubiquity of BPA exposure, its regrettable substitution with BPS and other structural analogs with similar reprotoxic potential, and that prevention strategies are needed to advance preconception care. While future studies should validate these associations, it may be prudent to inform couples planning conception about measures to reduce EDC exposure.

6. Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

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CRediT authorship contribution statement

Vicente Mustieles: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Yu Zhang:** Software, Formal analysis, Validation, Visualization, Writing - review & editing. **Jennifer Yland:** Writing - review & editing. **Joseph M. Braun:** Writing - review & editing. **Paige L. Williams:** Methodology, Writing - review & editing. **Blair J. Wylie:** Writing - review & editing. **Jill A. Attaman:** Writing - review & editing. **Jennifer B. Ford:** Project administration, Resources. **Alexandra Azevedo:** Project administration. **Antonia M. Calafat:** Writing - review & editing, Data curation. **Russ Hauser:** Writing - review & editing, Funding acquisition. **Carmen Messerlian:** Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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References

ACOG, 2014. Committee opinion no 611: method for estimating due date. Obstet. Gynecol. 124, 863–6. https://doi.org/10.1097/01.AOG.0000454932.15177.be.

Aker, A.M., Ferguson, K.K., Rosario, Z.Y., Mukherjee, B., Alshawabkeh, A.N., Cordero, J.F., Meeker, J.D., 2019. The associations between prenatal exposure to triclocarban, phenols and parabens with gestational age and birth weight in northern Puerto Rico. Environ. Res. 169, 41–51. https://doi.org/10.1016/j.envres.2018.10.030.

Aung, M.T., Ferguson, K.K., Cantonwine, D.E., McElrath, T.F., Meeker, J.D., 2019. Preterm birth in relation to the bisphenol A replacement, bisphenol S, and other phenols and parabens. Environ. Res. 169, 131–138. https://doi.org/10.1016/j.envres.2018.10.037.

Behnia, F., Peltier, M., Getahun, D., Watson, C., Saade, G., Menon, R., 2016. High bisphenol A (BPA) concentration in the maternal, but not fetal, compartment increases the risk of spontaneous preterm delivery. J. Matern. Neonatal Med. 29, 3583–3589. https://doi.org/10.3109/14767058.2016.1139570.

Bellavia, A., Mitro, S.D., Hauser, R., James-Todd, T., 2019. Paternal bias: the impact of not accounting for paternal confounders in reproductive epidemiological studies. Am. J. Obstet. Gynecol. https://doi.org/10.1016/j.ajog.2019.08.005.

Braun, J.M., Messerlian, C., Hauser, R., 2017. Fathers matter: why it's time to consider the impact of paternal environmental exposures on children's health. Curr. Epidemiol. Reports 4, 46–55. https://doi.org/10.1007/s40471-017-0098-8.

Buckley, J.P., Doherty, B.T., Keil, A.P., Engel, S.M., 2017. Statistical approaches for estimating sex-specific effects in endocrine disruptors research. Environ. Health Perspect. 125, 067013. https://doi.org/10.1289/EHP334.

Campen, K.A., Kucharczyk, K.M., Bogin, B., Ehrlich, J.M., Combelles, C.M.H., 2018. Spindle abnormalities and chromosome misalignment in bovine oocytes after exposure to low doses of bisphenol A or bisphenol S. Hum. Reprod. 33, 895–904. https://doi.org/10.1093/humrep/dey050.

Cantonwine, D., Meeker, J.D., Hu, H., Sánchez, B.N., Lamadrid-Figueroa, H., Mercado-García, A., Fortenberry, G.Z., Calafat, A.M., Téllez-Rojo, M.M., 2010. Bisphenol a exposure in Mexico city and risk of prematurity: a pilot nested case control study. Environ. Heal. 9, 62. https://doi.org/10.1186/1476-069X-9-62.

Cantonwine, D.E., Ferguson, K.K., Mukherjee, B., McElrath, T.F., Meeker, J.D., 2015. Urinary bisphenol a levels during pregnancy and risk of preterm birth. Environ. Health Perspect. 123, 895–901. https://doi.org/10.1289/ehp.1408126.

Carvaillo, J.-C., Barouki, R., Coumoul, X., Audouze, K., 2019. Linking bisphenol S to adverse outcome pathways using a combined text mining and systems biology approach. Environ. Health Perspect. 127, 047005. https://doi.org/10.1289/EHP4200.

Chawanpaiboon, S., Vogel, J.P., Moller, A.-B., Lumbiganon, P., Petzold, M., Hogan, D., Landoulsi, S., Jampathong, N., Kongwattanakul, K., Laopaiboon, M., Lewis, C., Rattanakanokchai, S., Teng, D.N., Thinkhamrop, J., Watananirun, K., Zhang, J., Zhou, W., Gülmezoglu, A.M., 2019. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. Lancet. Glob. Heal. 7, e37–e46. https://doi.org/10.1016/S2214-109X(18)30451-0.

Delnord, M., Zeitlin, J., 2019. Epidemiology of late preterm and early term births – an international perspective. Semin. Fetal Neonatal Med. 24, 3–10. https://doi.org/10.1016/j.siny.2018.09.001.

ECHA, 2016. ECHA. Member State Committee Support Document for Identification of 4, 4'-Isopropylidenediphenol (Bisphenol A) as a Substance of Very High Concern Because of its Toxic For Reproduction (Article 57 C), EC 201-245-8, CAS 80-05-7.

EFCNI, 2010. Too little, too late? Why Europe should do more for preterm infants. https://www.efcni.org/wp-content/uploads/2018/03/EFCNI_report_light_copyright.pdf (accessed 6.18.19).

Ferguson, K.K., Chin, H.B., 2017. Environmental chemicals and preterm birth: Biological mechanisms and the state of the science. Curr. Epidemiol. Rep. 4, 56–71. https://doi.org/10.1007/s40471-017-0099-7.

Ferguson, K.K., Colacino, J.A., Lewis, R.C., Meeker, J.D., 2017. Personal care product use among adults in NHANES: associations between urinary phthalate metabolites and phenols and use of mouthwash and sunscreen. J. Expo. Sci. Environ. Epidemiol. 27, 326–332. https://doi.org/10.1038/jes.2016.27.

Frederiksen, H., Jensen, T.K., Jørgensen, N., Kyhl, H.B., Husby, S., Skakkebæk, N.E., Main, K.M., Juul, A., Andersson, A.-M., 2014. Human urinary excretion of non-persistent environmental chemicals: an overview of Danish data collected between 2006 and 2012. Reproduction 147, 555–565. https://doi.org/10.1530/REP-13-0522.

Freire, C., Molina-Molina, J.-M., Iribarne-Durán, L.M., Jiménez-Díaz, I., Vela-Soria, F., Mustieles, V., Arrebola, J.P., Fernández, M.F., Artacho-Cordón, F., Olea, N., 2019. Concentrations of bisphenol A and parabens in socks for infants and young children in Spain and their hormone-like activities. Environ. Int. 127, 592–600. https://doi.org/10.1016/j.envint.2019.04.013.

Ghazipura, M., McGowan, R., Arslan, A., Hossain, T., 2017. Exposure to benzophenone-3 and reproductive toxicity: a systematic review of human and animal studies. Reprod. Toxicol. 73, 175–183. https://doi.org/10.1016/j.reprotox.2017.08.015.

Giulivo, M., Lopez de Alda, M., Capri, E., Barceló, D., 2016. Human exposure to endocrine disrupting compounds: their role in reproductive systems, metabolic syndrome and breast cancer a review. Environ. Res. 151, 251–264. https://doi.org/10.1016/j.envres.2016.07.011.

Hornung, R.L., 1990. Estimation of average concentration in the presence of non-detectable values. Appl. Ocuupational Environ. Hyg. 5, 46–51.

Huo, W., Xia, W., Wu, C., Zhu, Y., Zhang, B., Wan, Y., Zhou, A., Qian, Z., Chen, Z., Jiang, Y., Liu, H., Hu, J., Xu, B., Xu, S., Li, Y., 2018. Urinary level of triclosan in a population of Chinese pregnant women and its association with birth outcomes. Environ. Pollut. 233, 872–879. https://doi.org/10.1016/j.envpol.2017.08.073.

Jamal, A., Rastkari, N., Dehghaniathar, R., Aghaei, M., Nodehi, R.N., Nasseri, S., Kashani, H., Yunesian, M., 2019. Prenatal exposure to parabens and anthropometric birth outcomes: a systematic review. Environ. Res. 173, 419–431. https://doi.org/10.1016/j.envres.2019.02.044.

Johnson, P.I., Koustas, E., Vesterinen, H.M., Sutton, P., Atchley, D.S., Kim, A.N., Campbell, M., Donald, J.M., Sen, S., Bero, L., Zeise, L., Woodruff, T.J., 2016. Application of the navigation guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environ. Int. 92–93, 716–728. https://doi.org/10.1016/j.envint.2016.03.009.

Kataria, A., Levine, D., Wertenteil, S., Vento, S., Xue, J., Rajendiran, K., Kannan, K., Thurman, J.M., Morrison, D., Brody, R., Urbina, E., Attina, T., Trasande, L., Trachtman, H., 2017. Exposure to bisphenols and phthalates and association with oxidant stress, insulin resistance, and endothelial dysfunction in children. Pediatr. Res. 81, 857–864. https://doi.org/10.1038/pr.2017.16.

Liao, C., Kannan, K., 2014. Widespread occurrence of benzophenone-type UV light filters in personal care products from China and the United States: an assessment of human exposure. Environ. Sci. Technol. 48, 4103–4109. https://doi.org/10.1021/es405450n.

Luderer, U., Eskenazi, B., Hauser, R., Korach, K.S., McHale, C.M., Moran, F., Rieswijk, L., Solomon, G., Udagawa, O., Zhang, L., Zlatnik, M., Zeise, L., Smith, M.T., 2019. Proposed key characteristics of female reproductive toxicants as an approach for organizing and evaluating mechanistic data in hazard assessment. Environ. Health Perspect. 127, 75001. https://doi.org/10.1289/EHP4971.

Mani, S., Ghosh, J., Lan, Y., Senapati, S., Ord, T., Sapienza, C., Coutifaris, C., Mainigi, M., 2018. Epigenetic changes in preterm birth placenta suggest a role for ADAMTS genes in spontaneous preterm birth. Hum. Mol. Genet. 28, 84–95. https://doi.org/10.1093/hmg/ddy325.

Meeker, J.D., Yang, T., Ye, X., Calafat, A.M., Hauser, R., 2011. Urinary concentrations of parabens and serum hormone levels, semen quality parameters, and sperm DNA damage. Environ. Health Perspect. 119, 252–257. https://doi.org/10.1289/ehp.1002238.

Menon, R., Conneely, K.N., Smith, A.K., 2012. DNA methylation: an epigenetic risk factor in preterm birth. Reprod. Sci. 19, 6–13. https://doi.org/10.1177/1933719111424446.

Messerlian, C., Mustieles, V., Minguez-Alarcon, L., Ford, J.B., Calafat, A.M., Souter, I., Williams, P.L., Hauser, R., 2018a. Preconception and prenatal urinary concentrations of phenols and birth size of singleton infants born to mothers and fathers from the environment and reproductive health (EARTH) study. Environ. Int. 114. https://doi.org/10.1016/j.envint.2018.02.017.

Messerlian, C., Mustieles, V., Wylie, B.J., Ford, J.B., Keller, M., Ye, X., Calafat, A.M., Williams, P.L., Hauser, R., Environment Team Reproductive Health Study, 2017. Ultrasound gel as an unrecognized source of exposure to phthalates and phenols among pregnant women undergoing routine scan. Int. J. Hyg. Environ. Health 220, 1285–1294. https://doi.org/10.1016/j.ijheh.2017.08.003.

Messerlian, C., Williams, P.L., Ford, J.B., Chavarro, J.E., Mínguez-Alarcón, L., Dadd, R., Braun, J.M., Gaskins, A.J., Meeker, J.D., James-Todd, T., Chiu, Y.-H., Nassan, F.L., Souter, I., Petrozza, J., Keller, M., Toth, T.L., Calafat, A.M., Hauser, R., 2018b. The environment and reproductive health (EARTH) study: a prospective preconception cohort. Hum. Reprod. Open 1–11. https://doi.org/10.1093/hropen/hoy001.

Mínguez-Alarcón, L., Messerlian, C., Bellavia, A., Gaskins, A.J., Chiu, Y.H., Ford, J.B., Azevedo, A.R., Petrozza, J.C., Calafat, A.M., Hauser, R., Williams, P.L., 2019. Urinary concentrations of bisphenol A, parabens and phthalate metabolite mixtures in relation to reproductive success among women undergoing in vitro fertilization. Environ. Int. 126, 355–362. https://doi.org/10.1016/j.envint.2019.02.025.

Molina-Molina, J.M., Jiménez-Díaz, I., Fernández, M.F., Rodriguez-Carrillo, A., Peinado, F.M., Mustieles, V., Barouki, R., Piccoli, C., Olea, N., Freire, C., 2019. Determination of bisphenol A and bisphenol S concentrations and assessment of estrogen- and anti-androgen-like activities in thermal paper receipts from Brazil, France, and Spain. Environ. Res. 170, 406–415. https://doi.org/10.1016/j.envres.2018.12.046.

Mustieles, V., Pérez-Lobato, R., Olea, N., Fernández, M.F., 2015. Bisphenol A: Human exposure and neurobehavior. Neurotoxicology. https://doi.org/10.1016/j.neuro.2015.06.002.

Mustieles, V., Williams, P.L., Fernandez, M.F., Mínguez-Alarcón, L., Ford, J.B., Calafat, A.M., Hauser, R., Messerlian, C., 2018. Maternal and paternal preconception exposure to bisphenols and size at birth. Hum. Reprod. 33, 1528–1537. https://doi.org/10.1093/humrep/dey234.

Nevoral, J., Kolinko, Y., Moravec, J., Žalmanová, T., Hošková, K., Prokešová, Š., Klein, P., Ghaibour, K., Hošek, P., Štiavnická, M., Řimnáčová, H., Tonar, Z., Petr, J., Králíčková, M., 2018. Long-term exposure to very low doses of bisphenol S affects female reproduction. Reproduction 156, 47–57. https://doi.org/10.1530/REP-18-0092.

Nowak, K., Ratajczak-Wrona, W., Górska, M., Jabłońska, E., 2018. Parabens and their effects on the endocrine system. Mol. Cell. Endocrinol. 474, 238–251. https://doi.org/10.1016/j.mce.2018.03.014.
Park, C.J., Nah, W.H., Lee, J.E., Oh, Y.S., Gye, M.C., 2012. Butyl paraben-induced changes in DNA methylation in rat epididymal spermatozoa. Andrologia 44, 187–193. https://doi.org/10.1111/j.1439-0272.2011.01162.x.
Pearson, M.A., Lu, C., Schmotzer, B.J., Waller, L.A., Riederer, A.M., 2009. Evaluation of physiological measures for correcting variation in urinary output: implications for assessing environmental chemical exposure in children. J. Expo. Sci. Environ. Epidemiol. 19, 336–342. https://doi.org/10.1038/jes.2008.48.
Peretz, J., Vrooman, L., Ricke, W.A., Hunt, P.A., Ehrlich, S., Hauser, R., Padmanabhan, V., Taylor, H.S., Swan, S.H., VandeVoort, C.A., Flaws, J.A., 2014. Bisphenol a and reproductive health: update of experimental and human evidence, 2007–2013. Environ. Health Perspect. 122, 775–786. https://doi.org/10.1289/ehp.1307728.
Perrier, F., Giorgis-Allemand, L., Slama, R., Philippat, C., 2016. Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. Epidemiology 27, 378–388. https://doi.org/10.1097/EDE.0000000000000460.
Porpora, M., Piacenti, I., Scaramuzzino, S., Masciullo, L., Rech, F., Benedetti Panici, P., 2019. Environmental contaminants exposure and preterm birth: a systematic review. Toxics 7, 11. https://doi.org/10.3390/toxics7010011.
Rochester, J.R., Bolden, A.L., 2015. Bisphenol S and F: A systematic review and comparison of the hormonal activity of bisphenol a substitutes. Environ. Health Perspect. 123, 643–650. https://doi.org/10.1289/ehp.1408989.
Romero, R., Dey, S.K., Fisher, S.J., 2014. Preterm labor: one syndrome, many causes. Science 345 (80), 760–765. https://doi.org/10.1126/science.1251816.
Rosenfeld, C.S., 2015. Sex-specific placental responses in fetal development. Endocrinology. https://doi.org/10.1210/en.2015-1227.
Rubens, C.E., Sadovsky, Y., Muglia, L., Gravett, M.G., Lackritz, E., Gravett, C., 2014. Prevention of preterm birth: Harnessing science to address the global epidemic. Sci. Transl. Med. https://doi.org/10.1126/scitranslmed.3009871.
Samarasinghe, S.V.A.C., Krishnan, K., Naidu, R., Megharaj, M., Miller, K., Fraser, B., Aitken, R.J., 2018. Parabens generate reactive oxygen species in human spermatozoa. Andrology 6, 532–541. https://doi.org/10.1111/andr.12499.
Santangeli, S., Maradonna, F., Olivotto, I., Piccinetti, C.C., Gioacchini, G., Carnevali, O., 2017. Effects of BPA on female reproductive function: The involvement of epigenetic mechanism. Gen. Comp. Endocrinol. 245, 122–126. https://doi.org/10.1016/j.ygcen.2016.08.010.
Savitz, D.A., Terry, J.W., Dole, N., Thorp, J.M., Siega-Riz, A.M., Herring, A.H., 2002. Comparison of pregnancy dating by last menstrual period, ultrasound scanning, and their combination. Am. J. Obstet. Gynecol. 187, 1660–1666. https://doi.org/10.1067/mob.2002.127601.
Shi, M., Sekulovski, N., MacLean, J.A., Whorton, A., Hayashi, K., 2019a. Prenatal exposure to bisphenol a analogues on female reproductive functions in mice. Toxicol. Sci. 168, 561–571. https://doi.org/10.1093/toxsci/kfz014.
Shi, M., Whorton, A.E., Sekulovski, N., MacLean, J.A., Hayashi, K., 2019b. Prenatal exposure to bisphenol A, E and S induces transgenerational effects on female reproductive functions in mice. Toxicol. Sci. https://doi.org/10.1093/toxsci/kfz124.
Smarr, M.M., Grantz, K.L., Sundaram, R., Maisog, J.M., Kannan, K., Louis, G.M.B., 2015. Parental urinary biomarkers of preconception exposure to bisphenol A and phthalates in relation to birth outcomes. Environ. Heal. 14, 73. https://doi.org/10.1186/s12940-015-0060-5.
Suvorov, A., Waxman, D.J., 2015. Early programing of uterine tissue by bisphenol a: critical evaluation of evidence from animal exposure studies. Reprod. Toxicol. 57, 59–72. https://doi.org/10.1016/j.reprotox.2015.05.008.
Tang, R., Chen, M., Ding, G., Chen, X., Han, X., Zhou, K., Chen, L., Xia, Y., Tian, Y., Wang, X., 2013. Associations of prenatal exposure to phenols with birth outcomes. Environ. Pollut. 178, 115–120. https://doi.org/10.1016/j.envpol.2013.03.023.
Textor, J., van der Zander, B., Gilthorpe, M.S., Liskiewicz, M., Ellison, G.T., 2016. Robust causal inference using directed acyclic graphs: the R package "dagitty". Int. J. Epidemiol. 45, 1887–1894. https://doi.org/10.1093/ije/dyw341.
Toivonen, K.I., Oinonen, K.A., Duchene, K.M., 2017. Preconception health behaviours: a scoping review. Prev. Med. (Baltim) 96, 1–15. https://doi.org/10.1016/j.ypmed.2016.11.022.
Trasande, L., 2017. Exploring regrettable substitution: replacements for bisphenol A. Lancet. Planet. Heal. 1, e88–e89. https://doi.org/10.1016/S2542-5196(17)30046-3.
Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, D.R., Lee, D.-H., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T., Myers, J.P., 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr. Rev. 33, 378–455. https://doi.org/10.1210/er.2011-1050.
Vandenberg, L.N., Hauser, R., Marcus, M., Olea, N., Welshons, W.V., 2007. Human exposure to bisphenol A (BPA). Reprod. Toxicol. 24, 139–177. https://doi.org/10.1016/j.reprotox.2007.07.010.
von Goetz, N., Pirow, R., Hart, A., Bradley, E., Poças, F., Arcella, D., Lillegard, I.T.L., Simoneau, C., van Engelen, J., Husoy, T., Theobald, A., Leclercq, C., 2017. Including non-dietary sources into an exposure assessment of the European food safety authority: the challenge of multi-sector chemicals such as bisphenol A. Regul. Toxicol. Pharm. 85, 70–78. https://doi.org/10.1016/j.yrtph.2017.02.004.
Wan, Y., Huo, W., Xu, S., Zheng, T., Zhang, B., Li, Y., Zhou, A., Zhang, Y., Hu, J., Zhu, Y., Chen, Z., Lu, S., Wu, C., Jiang, M., Jiang, Y., Liu, H., Yang, X., Xia, W., 2018. Relationship between maternal exposure to bisphenol S and pregnancy duration. Environ. Pollut. 238, 717–724. https://doi.org/10.1016/j.envpol.2018.03.057.
WHO, 2012. The Global Action Report on Preterm Birth Born Too Soon. https://apps.who.int/iris/bitstream/handle/10665/44864/9789241503433_eng.pdf?sequence=1 (accessed 6.18.19).
Wu, L.-H., Zhang, X.-M., Wang, F., Gao, C.-J., Chen, D., Palumbo, J.R., Guo, Y., Zeng, E.Y., 2018. Occurrence of bisphenol S in the environment and implications for human exposure: a short review. Sci. Total Environ. 615, 87–98. https://doi.org/10.1016/j.scitotenv.2017.09.194.
Xin, F., Susiarjo, M., Bartolomei, M.S., 2015. Multigenerational and transgenerational effects of endocrine disrupting chemicals: a role for altered epigenetic regulation? Semin. Cell Dev. Biol. 43, 66–75. https://doi.org/10.1016/j.semcdb.2015.05.008.
Ye, X., Wong, L.-Y., Kramer, J., Zhou, X., Jia, T., Calafat, A.M., 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. https://doi.org/10.1021/acs.est.5b02135.
Ye, Y., Tang, Y., Xiong, Y., Feng, L., Li, X., 2019. Bisphenol A exposure alters placentation and causes preeclampsia-like features in pregnant mice involved in reprogramming of DNA methylation of *WNT2*. FASEB J. 33, 2732–2742. https://doi.org/10.1096/fj.201800934RRR.
Žalmanová, T., Hošková, K., Nevoral, J., Adámková, K., Kott, T., Šulc, M., Kotíková, Z., Prokešová, Š., Jílek, F., Králíčková, M., Petr, J., 2017. Bisphenol S negatively affects the meotic maturation of pig oocytes. Sci. Rep. 7, 485. https://doi.org/10.1038/s41598-017-00570-5.
Zama, A.M., Uzumcu, M., 2010. Epigenetic effects of endocrine-disrupting chemicals on female reproduction: An ovarian perspective. Front. Neuroendocrinol. 31, 420–439. https://doi.org/10.1016/j.yfrne.2010.06.003.
Zamkowska, D., Karwacka, A., Jurewicz, J., Radwan, M., 2018. Environmental exposure to non-persistent endocrine disrupting chemicals and semen quality: an overview of the current epidemiological evidence. Int. J. Occup. Med. Environ. Health 31, 377–414. https://doi.org/10.13075/ijomeh.1896.01195.
Zhou, X., Kramer, J.P., Calafat, A.M., Ye, X., 2014. Automated on-line column-switching high performance liquid chromatography isotope dilution tandem mass spectrometry method for the quantification of bisphenol A, bisphenol F, bisphenol S, and 11 other phenols in urine. J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 944, 152–156. https://doi.org/10.1016/j.jchromb.2013.11.009.
Zoeller, R.T., Brown, T.R., Doan, L.L., Gore, A.C., Skakkebaek, N.E., Soto, A.M., Woodruff, T.J., Vom Saal, F.S., 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from the endocrine society. Endocrinology 153, 4097–4110. https://doi.org/10.1210/en.2012-1422.