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Phthalate and DINCH urinary concentrations across pregnancy and risk of preterm birth

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ABSTRACT

Preconception and prenatal exposure to phthalates has been associated with an increased risk of preterm birth. However, it is unclear whether there are periods of heightened susceptibility during pregnancy. This prospective cohort study included 386 women undergoing fertility treatment who gave birth to a singleton infant during 2005 through 2018. Eleven phthalate metabolites were measured in spot urine samples collected at each trimester. In approximately 50% of participants, two metabolites of 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH), a phthalate substitute, were also measured. The molar sum of four di(2-ethylhexyl) phthalate metabolites (∑DEHP) was calculated. We evaluated the associations of mean maternal biomarker concentrations with risk of preterm birth using modified log-binomial models and utilized multiple informant models to compare trimester-specific associations. We examined the relative biomarker concentration across gestation comparing women with preterm birth to women with term delivery using quadratic mixed model. The risk ratio for preterm birth associated with a one-unit increase in the natural log-transformed urinary concentrations of ∑DEHP (mean during pregnancy) was 1.21 (95% confidence interval (CI): 0.84, 1.72). In multiple informant models, these associations were strongest in the third trimester (RR = 1.51; 95% CI: 1.17, 1.95). Estimated mean ∑DEHP concentrations were higher among women with preterm than term delivery, especially late in gestation. Associations with preterm birth were also observed for each of the four individual DEHP metabolites. Detection of cyclohexane-1,2-dicarboxylic acid monocarboxyisooctyl ester (MCOCH), a metabolite of DINCH, appeared to be positively related to preterm birth. In this prospective cohort of subfertile couples, maternal ∑DEHP metabolite concentrations during pregnancy were associated with an increased risk of preterm birth, particularly during late gestation.

1. Introduction

Preterm birth is a leading cause of infant morbidity and mortality worldwide (Goldenberg et al., 2008; Luu et al., 2017; Marlow et al., 2005), and approximately 10% of infants are born preterm each year in the United States in 2018 (Martin et al., 2019). While the underlying pathophysiology of this condition remains poorly understood, a multitude of environmental risk factors have been identified (Goldenberg et al., 2008). For example, prenatal exposure to endocrine disrupting chemicals (EDCs) has been associated with preterm birth (Cantonwine et al., 2010; Ferguson and Chin, 2017; Meeker, 2012; Porpora et al., 2019; Wigle et al., 2008). Of particular concern, phthalates comprise a

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family of EDCs widely used as plasticizers in personal care, food packaging and consumer products (Centers for Disease Control and Prevention, 2013), resulting in ubiquitous population exposure with more than 95% of North Americans presenting quantifiable urinary concentrations (Centers for Disease Control and Prevention, 2013; Hauser and Calafat, 2005; Zota et al., 2014). Phthalates can cross the placental barrier (Latini et al., 2003) and they have been demonstrated to exert anti-androgenic effects, in addition to other endocrine modes of action (Baken et al., 2019; Benjamin et al., 2017; Borch et al., 2006; Ferguson et al., 2017). Concerns about phthalate toxicity has prompted the use of 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) as an alternative plasticizer (Silva et al., 2013b). However, DINCH metabolites are also biologically active(Engel et al., 2018) and their potential effects on perinatal outcomes are poorly understood. To the best of our knowledge, no study has evaluated the relationship between maternal exposure to DINCH during pregnancy and preterm birth.

Several studies have reported an increased risk of preterm birth or shorter gestational length with higher maternal phthalate concentrations, measured in urine samples collected during pregnancy or umbilical cord blood collected at birth (Boss et al., 2018; Ferguson et al., 2014b; Ferguson et al., 2014c; Gao et al., 2019a; Huang et al., 2014; Yaghjyan et al., 2016). One publication reported no association between gestational age at delivery and urinary concentrations of di (2-ethylhexyl) phthalate (DEHP) or high molecular weight phthalate (MWP) metabolites during late pregnancy, but a modest positive association with low MWP concentrations (Wolff et al., 2008). Another study reported that first trimester urinary phthalates were not associated with preterm birth (Hu et al., 2020). Some inconsistencies in these findings may be due to variations in the timing of exposure assessment. Studies which investigated the vulnerable periods of phthalate exposure during pregnancy for preterm birth reported inconsistent results (Ferguson et al., 2014b; Gao et al., 2019b; Santos et al., 2021). One nested case-control study in the U.S. reported positive associations between phthalates exposure at early and late pregnancy and preterm birth (Ferguson et al., 2014b), while a Chinese cohort study found phthalate exposure in the second trimester was associated with increased odds of preterm birth (Gao et al., 2019b). A large Dutch cohort reported no trimester-specific associations for phthalate exposure and preterm birth (Santos et al., 2021). These studies utilized traditional logistic regression models to investigate trimester-specific associations and did not account for the potential selection bias by incomplete exposure data at each trimester (Ferguson et al., 2014b; Gao et al., 2019b; Santos et al., 2021).

The present study was designed to investigate the association between maternal urinary concentrations of phthalate and phthalate alternative metabolites and the risk of preterm birth, and to consider potential windows of heightened susceptibility using three complementary statistical approaches and accounting for potential selection bias. This study was conducted within the Environment and Reproductive Health (EARTH) Study.

2. Material and methods

2.1. Study population

The EARTH Study is a prospective cohort study of couples who sought treatment for infertility at the Massachusetts General Hospital (MGH) Fertility Center from 2004 through 2019. The EARTH Study followed couples during treatment and throughout the course of pregnancy. The study design and implementation have been described previously (Messerlian et al., 2018). Among 538 participants who gave birth during 2005 to and 2018, 446 (82.9%) had a singleton infant. The present analysis included 386 female participants, aged 18–46, who gave birth to a singleton infant between 2005 and 2018 and for whom we measured concentrations of phthalate and/or DINCH metabolites in at least one urine sample collected during pregnancy. Inclusion and exclusion criteria are detailed in Fig. 1. Trained research staff explained

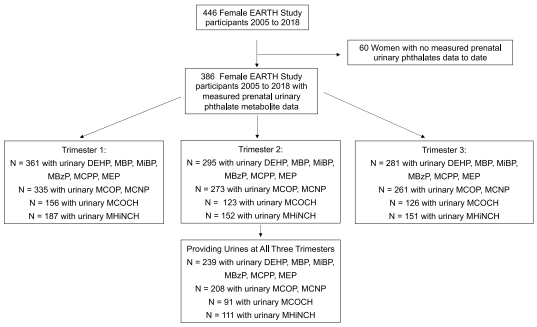

Fig. 1. Participant flow-chart and phthalate and DINCH metabolite data available in the Environment and Reproductive Health (EARTH) study among women with singleton births from 2005 to 2018. Abbreviations: DINCH, di (isononyl)cyclohexane-1,2-dicarboxylate; DEHP, di(2-ethylhexyl) phthalate; MEP, monoethyl phthalate; MBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MCOP, monocarboxyisooctyl phthalate; MCNP, monocarboxyisononyl phthalate; MCOCH, cyclohexane-1,2-dicarboxylic acid monocarboxyisooctyl ester; MHiNCH, cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester.

all procedures and answered relevant questions prior to obtaining participants' informed consent. The study was approved by the Human Studies Institutional Review Boards of Massachusetts General Hospital, the Harvard T. H. Chan School of Public Health, and the Centers for Disease Control and Prevention (CDC).

2.2. Assessment of preterm birth

Preterm birth was defined as live birth prior to 37 completed weeks of gestation (259 days). Gestational age in days was abstracted from delivery records and validated according to guidelines published by the American College of Obstetricians and Gynecologists (ACOG) for dating births following medically assisted reproduction (American College of Obstetricians and Gynecologists, 2017). Because this study was conducted among couples undergoing fertility treatment, we were able to estimate gestational age with high accuracy using *in vitro* fertilization (IVF) protocol dates. Among pregnancies conceived via IVF, gestational age was estimated as (outcome date – embryo transfer date +14 days + cycle day of transfer) (Savitz et al., 2002). For non-IVF pregnancies (intrauterine insemination (IUI) and spontaneous conception), we estimated gestational age by subtracting the cycle start date from the date of delivery. In cases where the delivery record estimates (gold standard) differed from the clinically estimated age by greater than 6 days, we corrected the gestational age with additional chart verification (corrected for three infants).

2.3. Assessment of covariate data

At enrollment, questionnaires were administered to obtain data on maternal and paternal age, education, race, and smoking status. In addition, trained research study staff measured each patient's height and weight. Pre-pregnancy body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). The treating infertility physician diagnosed the underlying cause of infertility using guidelines defined by the Society for Assisted Reproductive Technology (SART) (ASRM Committee, 2015). We categorized infertility diagnoses as male factor, female factor, or unexplained, based on the patient's primary diagnosis. Method of infertility treatment for the conception cycle that resulted in live birth (the study pregnancy) was abstracted from medical records by research study staff. We dichotomized treatment as using assisted reproductive technology (ART; *e.g.*, fresh or frozen IVF protocols, including intracytoplasmic sperm injection) or non-ART (*e.g.*, IUI with or without ovulation induction/stimulation, ovulation

induction/stimulation with timed intercourse, or non-medically assisted/naturally conceived).

2.4. Assessment of phthalate and DINCH metabolites

Female participants provided one spot urine sample at study entry, up to two samples during each fertility treatment cycle, and one sample at each of three prenatal visits: early (median = 6 weeks' gestation), middle (median = 21 weeks), and late pregnancy (median = 34 weeks). Urine samples were collected into a sterile polypropylene cup and specific gravity was measured for each sample using a handheld refractometer (National Instrument Company, Inc., Baltimore, MD, USA). The samples were then aliquoted, frozen at $-80^{\circ}C$, and shipped overnight on dry ice to the CDC (Atlanta, GA, USA). Samples were analyzed via solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry (Silva et al., 2007; Silva et al., 2013a). To ensure the accuracy of the measurements, each analytical batch included low-concentration and high-concentration urine pools and reagent blanks as quality controls (Silva et al., 2007; Silva et al., 2013a). We measured the urinary concentrations of the following phthalate metabolites: mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono (2-ethyl-5-carboxypentyl) phthalate (MECPP); monoethyl phthalate (MEP); mono-n-butyl phthalate (MBP); mono-isobutyl phthalate (MiBP); monobenzyl phthalate (MBzP); mono(3-carboxypropyl) phthalate (MCPP); monocarboxyisooctyl phthalate (MCOP); and monocarboxyisononyl phthalate (MCNP). We also measured the urinary concentrations of two DINCH metabolites, cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester (MHiNCH) and cyclohexane-1, 2-dicarboxylic acid monocarboxyisooctyl ester (MCOCH), for participants who enrolled in the study after 2011 (Fig. 1). The limits of detection ranged from 0.1 to 1.0 μg/L. For metabolites detected in at least 65% of samples, unadjusted concentrations below the limit of detection were replaced with the limit of detection divided by $\sqrt{2}$ (Hornung and Reed, 1990). To account for urinary dilution, each biomarker concentration was multiplied by [(SGp − 1)/(SGi − 1)], where SGi is the specific gravity of the participant's sample and SGp is the mean specific gravity for all participants included in the study (mean = 1.015) (Pearson et al., 2009). Due to low detection rates (20–30%), the two DINCH metabolites were dichotomized as detected versus non detected.

The DEHP metabolites included MEHP, MEHHP, MEOHP, and MECPP. The molar sum of DEHP metabolites (∑DEHP) was calculated by dividing each metabolite concentration (μg/L) by its molecular weight (g/mol) and then summing across metabolites: ∑DEHP = ([MEHP]/278.34 + [MEHHP]/294.34 + [MEOHP]/292.33 + [MECPP]/308.33). We then multiplied the molar sum (μmol/L) by the molecular weight of MECPP (308.33 g/mol) to convert the units of ∑DEHP to μg/L. This improves the interpretability of ∑DEHP by making it comparable to the other phthalate metabolite concentrations.

To examine the potential effects of phthalates with known anti-androgenic properties, we calculated a summary measure of the anti-androgenic metabolites (i.e., MEHP, MEHHP, MEOHP, MECPP, MBP, MiBP, and MBzP) (Varshavsky et al., 2016). The summary estimate of the anti-androgenic phthalates (∑AAP) was calculated by multiplying the specific gravity-adjusted concentration of each metabolite by its anti-androgenic potency and summing the weighted concentrations: ∑AAP = ([MBP] + (0.24*[MiBP]) + (0.26*[MBzP]) + (0.61*[MEHP]) + (0.61*[MEHHP])+(0.61*[MEOHP])+ (0.61*[MECPP])) (Varshavsky et al., 2016). Potencies were based on the inverse of benchmark doses associated with a 5% reduction in rat fetal testis testosterone concentrations as described by the National Research Council, Phthalates and Cumulative Risk Assessment (National Research Council, 2008). In summary, we quantified 1) the specific gravity-adjusted urinary concentrations of eleven individual phthalate metabolites and detection of two DINCH metabolite concentrations, 2) the sum of the DEHP metabolites (∑DEHP), and 3) a composite measure of the anti-androgenic metabolites (∑AAP).

2.5. Statistical analysis

We natural log-transformed the specific gravity-adjusted urinary phthalate biomarker to reduce the influence of extreme values. Mean maternal urinary biomarker concentrations were estimated by averaging the natural log-transformed concentrations in all urine samples (1, 2 or 3) provided by the participant during pregnancy. To assess the correlations between measures of the same biomarker across trimesters and the temporal variability of maternal biomarker concentrations, we calculated Spearman and intraclass correlation coefficients (ICC).

We used three complementary analytical approaches to evaluate the associations between phthalate biomarker concentrations and preterm birth, with a particular focus on identifying the vulnerable windows across pregnancy. First, we evaluated the associations between mean maternal biomarker concentrations and preterm birth. We fit modified log-binomial regression models, specifying the log link function and Poisson distribution, to estimate the covariate-adjusted risk ratios (RRs) and 95% confidence intervals (CIs) for preterm birth for every natural log unit increase in mean maternal biomarker concentrations. Second, we evaluated the associations between trimester-specific biomarker concentrations and preterm birth using multiple informant models (Sánchez et al., 2011). This approach estimates associations between biomarker concentrations at each trimester and preterm birth simultaneously within the same model, facilitating comparison of the magnitudes of association across all three trimesters. We fit modified log-binomial multiple informant models with generalized estimating equations to estimate trimester-specific covariate-adjusted RRs and 95% CIs of preterm birth for each natural log unit increase in biomarker concentrations. We primarily considered differences in the parameter estimates and their confidence intervals between trimesters. However, we also conducted tests of heterogeneity and considered a *p*-value of <0.20 as supplemental evidence that the associations differed across trimesters. This test evaluates the null hypothesis that the coefficients are equal at each trimester, versus the alternative hypothesis that at least one trimester-specific coefficient differs from another. While the *p*-value offers valuable supplemental evidence in this context, we caution against interpreting the *p*-value without consideration of the confidence intervals. Last of all, we fit mixed effects models with linear and quadratic terms for gestational week of phthalate measurements to examine patterns of urinary phthalate metabolite concentrations among preterm vs. non-preterm births across gestational weeks. For this analysis, we present adjusted relative biomarker concentrations (*i.e.*, the estimated mean concentration of a biomarker among women with preterm birth divided by the estimated mean concentration of a biomarker among women with a term birth) and their 95% CIs across gestation.

The DINCH biomarker concentrations were dichotomized as above the limit of detection (detected, i.e. concentrations above 0.4 μg/L for MHiNCH and above 0.5 μg/L for MCOCH) versus below the limit of detection (not detected) for each sample. Maternal overall DINCH exposure was then categorized as detected (at least one sample during pregnancy had detectable concentrations of a DINCH metabolite) or not detected (no sample had detectable concentrations of DINCH metabolites). We compared the percentage of pregnancies with preterm birth among those with detectable versus non detectable concentrations of the DINCH biomarkers. We evaluated the adjusted relative detection rates across gestation for women with preterm versus term births using modified log-binomial regression with linear and quadratic terms for gestational week.

For all models, potential confounders were selected a priori based on substantive knowledge using a directed acyclic graph (eFigure 1). Covariates included: maternal age (years, continuous), BMI (kg/m^2,

continuous), education (≤college degree versus > college degree), smoking status (never smoked versus ever smoked), race (white versus non-white), and fertility treatment protocol (ART versus non-ART). All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

2.6. Sensitivity analysis

Because previous studies have presented evidence for effect modification by infant sex (Gao et al., 2019a; Huang et al., 2014), we fit stratified models for the trimester-specific analyses for the phthalate metabolites by infant sex. We also evaluated potential selection bias in the trimester-specific multiple informant analyses, as not all participants provided urine samples at every trimester. Selection bias may arise if the probability of providing a urine sample at each trimester is associated with both preterm birth (outcome) and urinary concentrations of phthalate metabolites (exposure). This mechanism is demonstrated in a directed acyclic graph (eFigure 1). We used inverse probability weighted estimation to account for this potential bias (Hernán et al., 2004). First, we estimated the probability of non-missingness (*i.e.*, having urine samples at all three trimesters) for each participant, conditional on study year, maternal age, BMI, education, race, parity, history of pregnancy loss, partner's participation in the study, preterm birth of the index pregnancy (because participants with shorter gestation may not have the opportunity to contribute the third urine sample), and a composite maternal risk variable. This composite variable was designed to reflect a broad risk profile that may be associated with follow-up and was based on evidence of diabetes (pre-existing or gestational), hypertension (pre-existing or gestational), preeclampsia, thrombophilia, placental abruption, cervical insufficiency, preterm labor or premature rupture of membranes, and intrauterine growth restriction. These data were obtained from delivery records. We then calculated weights for each participant equal to the inverse of the predicted probability of non-missingness. Lastly, we fit weighted multiple informant models among the 239 participants who provided urine samples at all trimesters. In the weighted models, each selected participant accounts for non-selected participants who had similar characteristics (*i.e.*, a similar probability of selection). Thus, the model is effectively fit within a pseudo-population that is unaffected by selection bias. Because parity and previous history of preterm birth might potentially confound the associations, we restricted the analyses to nulliparous participants as a sensitivity analysis. We supplemented the analyses of phthalates and preterm birth by exploring their relationships with gestational age as a continuous outcome.

3. Results

The 386 participants included in our analysis had an average age of 35 years and an average BMI of 24 kg/m^2 at study entry (Table 1). About 85% of women identified themselves as white, 87% had a college degree, and 25% had ever smoked. A majority (83%) were primiparous, 75% were diagnosed with female factor or unexplained infertility, and 57% conceived using ART. Among the 386 singleton infants, 52% were male, 4% had low birth weight (<2,500 g), and 8% were born preterm (Table 1). The distributions of specific gravity-adjusted log-transformed urinary concentrations of the phthalate and DINCH biomarkers are described in .eTable 1, We observed moderate to high detection rates for all urinary metabolites except MCOCH and MHiNCH, which had detection rates of 19–20% and 28%–30%, respectively. We observed weak to moderate correlations, based on ICC estimates, between measurements of the same phthalate metabolite across trimesters (eTable 2). We observed the least temporal variability for MiBP (ICC = 0.45), MEP (ICC = 0.50), and MBzP (ICC = 0.49).

The risk ratios for preterm birth associated with a one log unit increase in mean maternal biomarker concentrations were 1.21 for ∑DEHP (95% CI: 0.84, 1.72) and 1.18 for ∑AAP (95% CI: 0.81, 1.73) after adjusting for age, BMI, smoking status, education, race, and treatment protocol (Table 2). Results were similar for the four individual DEHP metabolites (MEHP, MEHHP, MEOHP, and MECPP). The adjusted risk ratios suggested a possible inverse association between mean maternal urinary biomarker concentrations and risk of preterm birth for MiBP (RR = 0.73; 95% CI: 0.47, 1.14), MCOP (RR = 0.88, 95% CI: 0.65, 1.20), and MCNP (RR = 0.78; 95% CI: 0.49, 1.26). The effect estimates for MEP, MBP, MBzP, and MCPP were very close to the null.

Table 1
Maternal and infant characteristics of 386 mothers with a singleton birth in the Environment and Reproductive Health (EARTH) Study (2005–2018).

Maternal Characteristics	N = 386
Age (years)	
Mean (SD)	34.7 (3.9)
Age>35, n (%)	158 (41)
Race, n (%)	
White	327 (85)
Black or African American	11 (3)
Asian	32 (8)
American Indian, Alaska Native, Native Hawaiian, or Pacific Islander	16 (4)
Body Mass Index (BMI, *Kg/m^2*)	
Mean (SD)	24.2 (4.3)
BMI >25, n (%)	125 (32)
Education, n (%)	
< College	52 (13)
College Graduate	127 (33)
Graduate Degree	207 (54)
Smoking Status, n (%)	
Never	290 (75)
Ever (former or current)	96 (25)
Infertility Diagnosis, n (%)	
Male Factor	97 (25)
Female Factor	124 (32)
Unexplained	165 (43)
Nulliparous, n (%)	321 (83)
Mode of conception [a], n (%)	
ART	219 (57)
Non-ART	167 (43)
Infant Characteristics	
Male, n (%)	200 (52)
Birth weight (grams)	
Mean (SD)	3352 (529)
Minimum-Maximum	1090–5040
Low birth weight (<2,500 g), n (%)	16 (4)
Gestational age at birth	
Mean (SD)	39.4 (1.7)
Minimum-Maximum	31–42
Preterm birth (<37 weeks' gestation), n (%)	31 (8)

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

Results from trimester-specific analyses using multiple informant models are presented in Table 3. We observed little or no association between urinary ∑DEHP concentrations and preterm birth in the first and second trimesters, but a positive association in the third trimester (RR = 1.51; 95% CI: 1.17, 1.95), though the *p*-value for the test of heterogeneity was not significant ($p = 0.24$). We observed similar results for ∑AAP and the individual DEHP metabolites. We also found positive associations between urinary concentrations of MBP and preterm birth especially in the third trimester, although these estimates were more modest, and imprecise. Urinary concentrations of MCNP were inversely associated with preterm birth at all trimesters, with the strongest association in the third trimester. There were no substantial differences across trimesters for urinary concentrations of MEP, MiBP, MBzP, MCPP, or MCOP.

The relative urinary concentrations of ∑DEHP comparing preterm with non-preterm births increased throughout pregnancy, with the largest relative concentration being 1.76 (95% CI: 0.94, 3.29) at the 36th

Table 2
Risk Ratios (RR) and 95% Confidence Intervals (95% CIs) for preterm birth per log-unit increase in mean prenatal urinary phthalate metabolite concentrations among 386 participants in the Environment and Reproductive Health (EARTH) Study, 2005–2018.

	Preterm birth	Unadjusted	Adjusted[a]
Phthalate Biomarker	n/N	RR (95% CI)	RR (95%CI)
∑DEHP [b]	31/386	1.26 (0.89, 1.79)	1.21 (0.84, 1.72)
∑AAP [c]	31/386	1.24 (0.85, 1.79)	1.18 (0.81, 1.73)
MEHP	31/386	1.23 (0.87, 1.73)	1.21 (0.86, 1.71)
MEHHP	31/386	1.28 (0.92, 1.79)	1.23 (0.88, 1.72)
MEOHP	31/386	1.31 (0.93, 1.83)	1.26 (0.90, 1.77)
MECPP	31/386	1.21 (0.85, 1.72)	1.16 (0.81, 1.66)
MEP	31/386	1.08 (0.81, 1.44)	1.08 (0.81, 1.45)
MBP	31/386	1.10 (0.73, 1.65)	1.07 (0.70, 1.64)
MiBP	31/386	0.73 (0.48, 1.13)	0.73 (0.47, 1.14)
MBzP	31/386	1.08 (0.76, 1.54)	1.08 (0.76, 1.54)
MCPP	31/386	1.02 (0.74, 1.40)	0.96 (0.69, 1.32)
MCOP	27/372	0.92 (0.67, 1.25)	0.88 (0.65, 1.20)
MCNP	27/372	0.89 (0.57, 1.40)	0.78 (0.49, 1.26)

Abbreviations: ∑DEHP, weighted molar sum of the di(2-ethylhexyl) phthalate metabolites; ∑AAP, summary measure of the anti-androgenic phthalates; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEP, monoethyl phthalate; MBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MCOP, monocarboxyisooctyl phthalate; MCNP, monocarboxyisononyl phthalate.

[a] Models adjusted for maternal age (years, continuous), BMI (Kg/m^2, continuous), education (≤college degree versus > college degree), smoking status (never smoked versus ever smoked), race (white versus non-white), and fertility treatment protocol (ART versus non-ART).

[b] ∑DEHP = 308 g/mol *([MEHP]*(1/278.34) + [MEHHP]*(1/294.34) + [MEOHP]*(1/292.33) + [MECPP]*(1/308.33)).

[c] ΣAAP = ([MBP] + (0.24*[MiBP]) + (0.26*[MBzP]) + (0.61*[MEHP]) + (0.61*[MEHHP]) + (0.61*[MEOHP])+ (0.61*[MECPP])).

gestational week (Fig. 2). We observed a similar but more modest trend for MBP. No consistent patterns were observed for the relative urinary concentrations of MEP, MiBP, MBzP, MCPP, MCOP, or MCNP between preterm and non-preterm births.

Urinary concentrations of MCOCH and MHiNCH were quantified in 183 and 216 women, respectively (eTable 4). Preterm birth occurred in 5 pregnancies (8.77%) out of 57 with detection of MCOCH in at least one sample during pregnancy, and 2 pregnancies (1.59%) out of 126 with no detection of MCOCH. Preterm birth occurred in 5 pregnancies (5.00%) out of 100 with detection of MHiNCH in at least one sample during pregnancy, and 7 pregnancies (6.03%) out of 116 with no detection of MHiNCH. The percentage of pregnancies with preterm birth was generally higher among those with MCOCH detected in each individual trimester. The number of preterm births for each group was too small to perform adjusted analyses. Our analysis of the relative detection among preterm births versus non-preterm births suggested elevated detection of MCOCH for preterm births, particularly during early and middle gestation after adjusting for covariates (Fig. 3). The highest point estimate (detection ratio) was 2.98 (95% CI: 1.19, 7.48) at gestational week 17. There was little difference in detection of MHiNCH between preterm births and non-preterm births at any point during gestation.

3.1. Sensitivity analysis

We observed some differences in the trimester-specific associations between male and female infants (eTable 3). Positive associations between third trimester phthalate metabolite concentrations and preterm birth were generally stronger among female compared to male infants. Results from trimester-specific analyses using inverse probability weighting to account for potential selection bias are presented in eTable 5. Consistent with the unweighted models, we observed the strongest associations in the third trimester for ∑DEHP (RR = 1.50; 95% CI: 1.15, 1.97), ∑AAP (RR = 1.51; 95% CI: 1.10, 2.08) and MCPP (RR = 1.16; 95% CI: 0.95, 1.40). In contrast, we observed the strongest associations in the second trimester for MEP, MBP, MBzP, MCOP, and MCNP. However, these findings were imprecise. Restricting the analyses to nulliparous women did not change the observed associations (eTable 6). Participants with MCOCH detected in any of their prenatal urine samples had shorter gestational age compared with those without MCOCH detection in all urine samples (−3.07 days, 95% CI: −6.48, 0.34). The associations were strongest for the first trimester (−5.36 days, 95% CI: −10.26, −0.46) (eTable 7). Similarly, participants with MHiNCH detected in their first trimester urine samples had a decrease in gestational age by 2.66 days (95% CI: −6.12, 0.80). No apparent associations

Table 3
Risk Ratios (RRs) and 95% Confidence Intervals (95% CIs) for preterm birth per log-unit increase in urinary phthalate metabolite concentrations by pregnancy trimester among 386 mothers in the Environment and Reproductive Health (EARTH) Study, 2005–2018, using multiple informant models.

	Trimester 1		Trimester 2		Trimester 3		Test of Heterogeneity
Phthalate Biomarker	N Preterm	RR[a] (95%CI)	N Preterm	RR[a] (95%CI)	N Preterm	RR[a] (95%CI)	*p-value* [b]
∑DEHP [c]	30/361	1.10 (0.87, 1.38)	25/295	1.00 (0.75, 1.34)	17/281	1.51 (1.17, 1.95)	0.24
∑AAP [d]	30/361	1.10 (0.85, 1.43)	25/295	0.99 (0.74, 1.32)	17/281	1.52 (1.13, 2.04)	0.27
MEHP	30/361	1.09 (0.88, 1.36)	25/295	0.98 (0.70, 1.36)	17/281	1.46 (1.14, 1.87)	0.24
MEHHP	30/361	1.11 (0.90, 1.37)	25/295	1.01 (0.77, 1.32)	17/281	1.50 (1.19, 1.89)	0.19
MEOHP	30/361	1.12 (0.90, 1.38)	25/295	1.03 (0.78, 1.35)	17/281	1.57 (1.24, 1.97)	0.16
MECPP	30/361	1.08 (0.86, 1.37)	25/295	0.99 (0.75, 1.30)	17/281	1.47 (1.10, 1.96)	0.32
MEP	30/361	1.01 (0.82, 1.26)	25/295	1.04 (0.82, 1.31)	17/281	1.02 (0.72, 1.44)	0.99
MBP	30/361	0.94 (0.60, 1.47)	25/295	1.13 (0.84, 1.52)	17/281	1.18 (0.77, 1.80)	0.77
MiBP	30/361	0.72 (0.47, 1.11)	25/295	0.85 (0.56, 1.30)	17/281	0.81 (0.50, 1.31)	0.59
MBzP	30/361	1.08 (0.77, 1.53)	25/295	1.15 (0.84, 1.58)	17/281	1.12 (0.78, 1.60)	0.86
MCPP	30/361	0.90 (0.71, 1.14)	25/295	0.96 (0.75, 1.23)	17/281	1.01 (0.79, 1.28)	0.83
MCOP	24/335	0.91 (0.70, 1.19)	20/273	0.92 (0.66, 1.29)	13/261	0.89 (0.60, 1.31)	0.86
MCNP	24/335	0.96 (0.69, 1.34)	20/273	0.77 (0.49, 1.23)	13/261	0.73 (0.39, 1.35)	0.58

Abbreviations: ∑DEHP, weighted molar sum of the di(2-ethylhexyl) phthalate metabolites; ∑AAP, summary measure of the anti-androgenic phthalates; MEHP, mono(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEP, monoethyl phthalate; MBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MCOP, monocarboxyisooctyl phthalate; MCNP, monocarboxyisononyl phthalate.

[a] Models adjusted for maternal age (years, continuous), BMI (kg/m2, continuous), education (≤college degree versus > college degree), smoking status (never smoked versus ever smoked), race (white versus non-white), and fertility treatment protocol (ART versus non-ART).

[b] *p-value* for test of homogeneity across trimesters.

[c] ∑DEHP = 308 g/mol *([MEHP]*(1/278.34) + [MEHHP]*(1/294.34) + [MEOHP]*(1/292.33) + [MECPP]*(1/308.33)).

[d] ΣAAP = ([MBP] + (0.24*[MiBP]) + (0.26*[MBzP]) + (0.61*[MEHP]) + (0.61*[MEHHP]) + (0.61*[MEOHP]) + (0.61*[MECPP])).

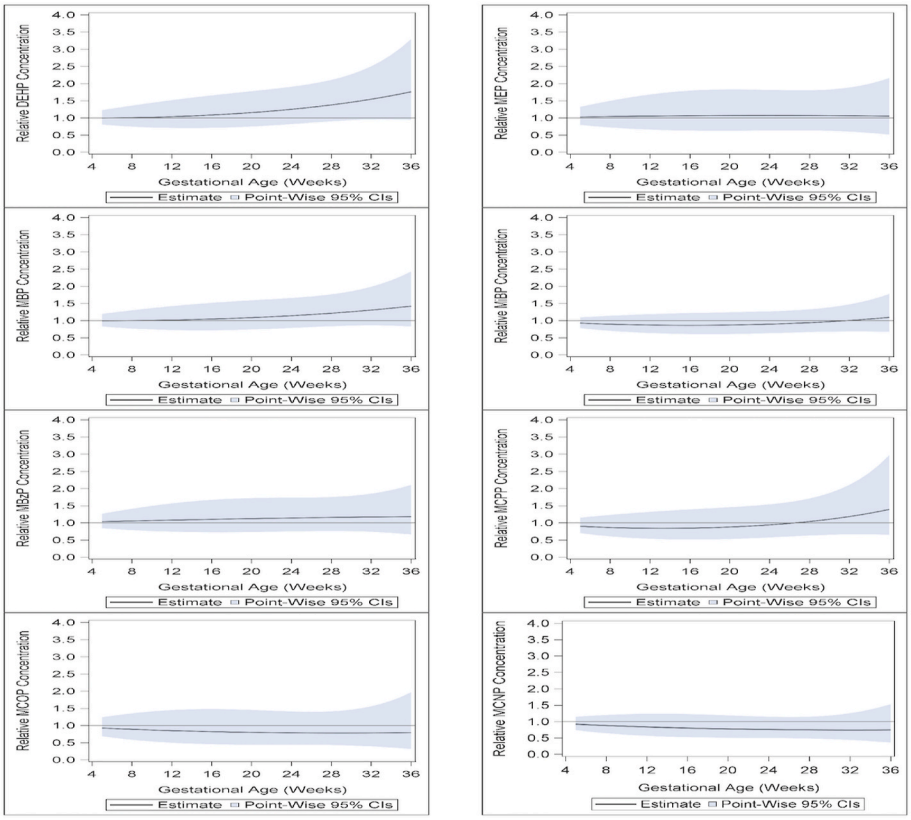

Fig. 2. Relative urinary concentrations [a] of phthalate metabolites comparing preterm to term births, across the duration of pregnancy, among 386 participants in the Environment and Reproductive Health (EARTH) Study, 2005–2018. Abbreviations: DEHP, weighted molar sum of the di(2-ethylhexyl) phthalate metabolites; MEP, monoethyl phthalate; MBP, mono-n-butyl phthalate; MiBP, mono-isobutyl phthalate; MBzP, monobenzyl phthalate; MCPP, mono(3-carboxy propyl) phthalate; MCOP, monocarboxyisooctyl phthalate; MCNP. [a] Relative urinary concentration for gestational week A was calculated as estimated concentration for preterm birth at gestational week A divided by the estimated concentration for non-preterm birth at gestational week A. Analyses were adjusted for maternal age (years, continuous), BMI (kg/m2, continuous), education (≤college degree versus > college degree), smoking status (never smoked versus ever smoked), race (white versus non-white), and fertility treatment protocol (ART versus non-ART).

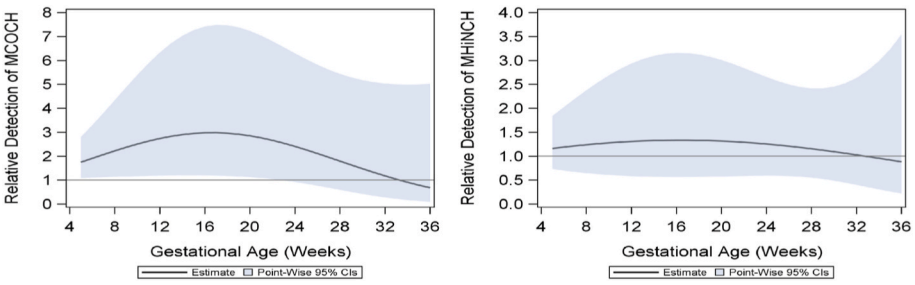

Fig. 3. Relative detection [a] of DINCH metabolites comparing preterm to term births, across the duration of pregnancy, among 386 participants in the Environment and Reproductive Health (EARTH) Study, 2005–2018. Abbreviations: DINCH, di(isononyl) cyclohexane-1,2-dicarboxylate; MCOCH, cyclohexane -1,2-dicarboxylic acid monocarboxyisooctyl ester; MHiNCH, cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester. [a] Relative detection for gestational week A was calculated as the percentage of samples with detected biomarker among preterm births at gestational week A divided the percentage of samples with detected biomarker among non-preterm births at gestational week A. Analyses were adjusted for maternal age (years, continuous), BMI (kg/m2, continuous), education (≤college degree versus > college degree), smoking status (never smoked versus ever smoked), race (white versus non-white), and fertility treatment protocol (ART versus non-ART).

were observed for the other phthalates biomarkers and gestational age (eTable 7).

4. Discussion

In this prospective cohort of couples undergoing fertility treatment, we evaluated the associations of maternal exposure during pregnancy to phthalates and phthalate substitutes with preterm birth, triangulating three complementary statistical approaches. Maternal urinary concentrations of ∑DEHP and ∑AAP were associated with a higher risk of preterm birth with the associations being strongest in the third trimester. Our findings also suggest that detectable urinary concentrations of MCOCH may be positively associated with preterm birth, but these results should be interpreted with caution due to the low detection frequencies of the DINCH biomarkers. Compared with pregnancies resulting in a term birth, those with preterm birth had higher concentrations of ∑DEHP across pregnancy, and they had higher detection rates of MHiNCH and MCOCH during early and middle gestation. Notably, the third trimester was identified as a potential critical window for ∑DEHP and ∑AAP. These associations seemed stronger among female infants as compared with male infants. The observed association between ∑AAP and preterm birth is likely driven by concentrations of the DEHP metabolites (MEHP, MEHHP, MEOHP, MECPP), and not by MBP, MiBP, or MBzP, which individually had small and inconsistent associations with preterm birth.

Our previous results in this same cohort indicated that maternal preconception exposure to DEHP and DINCH were positively associated with preterm birth risk (Zhang et al., 2020). While the preconception DEHP association remained unchanged after co-exposure adjustment for prenatal DEHP, the preconception DINCH association was attenuated when prenatal DINCH was accounted for (Zhang et al., 2020). In conjunction with the current results, we hypothesize that maternal preconception DEHP exposure may predispose to preterm birth, while continued DEHP exposure during pregnancy may cumulatively

contribute to this outcome, especially during the third trimester. While epigenetic mechanisms could explain preconception associations (Zhang et al., 2020), effects of DEHP during late pregnancy may be due to endocrine disruption (Baken et al., 2019), inflammation (Ferguson et al., 2014a), and/or increased oxidative stress. A recent mediation analysis by Ferguson et al. (2017) lends further support to this hypothesized pathway. For DINCH, altered implantation and placentation during the first trimester could be hypothesized. Although scant toxicological data are available for this emerging phthalate substitute, DINCH metabolites can bind to human nuclear receptors (Engel et al., 2018), and higher DINCH exposure was associated with lower estradiol peak levels and lower total oocyte yield among a subset of female EARTH participants (Mínguez-Alarcón et al., 2016).

Our findings are in agreement with several previous studies, which reported an increased risk of preterm birth or shorter gestational duration associated with maternal exposure to phthalates (Boss et al., 2018; Ferguson et al., 2014b; Ferguson et al. 2014c; Ferguson et al. 2019a; Gao et al., 2019a; Huang et al., 2014; Meeker et al., 2009; Santos et al., 2021; Weinberger et al., 2014; Whyatt et al., 2009; Yaghjyan et al., 2016). Specifically, in a nested case-control study of 130 preterm birth cases and 352 controls in Boston, Ferguson et al. (2014c) measured phthalate metabolite concentrations in up to four urine samples collected throughout pregnancy (Ferguson et al., 2014c). The authors reported robust associations between average prenatal and late pregnancy DEHP and MBP exposure and the risk of preterm birth. Another prospective cohort study conducted across four U.S. sites (n = 783) evaluated urinary phthalate concentrations at each trimester (Ferguson et al., 2019a). Third trimester DEHP was positively associated with odds of preterm birth, but no appreciable association was observed for average maternal DEHP nor for other phthalates metabolites. Similarly, a Chinese cohort study of 3,266 mother-infant pairs reported that third trimester DEHP exposure was associated with increased odds of preterm birth, and no associations were observed for other phthalate metabolites examined (Gao et al., 2019a). However, results from the Generation R study in the Netherlands (n = 1,379) indicated no appreciable associations for average maternal and trimester-specific phthalate exposure and preterm birth risk (Santos et al., 2021). However, women who failed to provide urine samples at every trimester were excluded, which could introduce selection bias. The urinary phthalate concentrations in this cohort were lower than our population, which could explain the differences in findings across studies. Of note, our population has similar or lower DEHP concentrations with cohorts of pregnant women in U.S. and Mexico, and with pregnant and non-pregnant women in the National Health and Nutrition Examination Survey (NHANES) 2007–2017 (Shin et al., 2020; Wu et al., 2020). Other studies that have evaluated maternal exposure during pregnancy to phthalates and continuous gestational length have reported inconsistent results (Chin et al., 2019; Shoaff et al., 2016; Wolff et al., 2008).

In the present study, we collected urine samples in the first, second, and third trimesters, and evaluated patterns in exposure biomarker concentrations across a wider range of gestation. We utilized three statistical approaches to robustly consider the associations of exposure to phthalates and phthalate substitutes with preterm birth throughout pregnancy. In addition, we employed inverse probability weighting to account for potential selection bias due to differences in the probability of providing a urine sample at all three trimesters. Further, we expect high accuracy in our estimation of gestational age, given that this study was conducted at a fertility center.

This study has several limitations. First, our ability to evaluate the relationships between DINCH metabolites and preterm birth was limited, as the detection rates were low (19–20% for MCOCH and 28–30% for MHiNCH) and the number of participants with DINCH measurements was small. In addition, the concentrations of DINCH metabolites were generally low, and their maximum values were only about 2–2.5 times higher than the limit of detection. Thus, results from these analyses should be interpreted cautiously and confirmed by future studies. However, we feel that these findings are important to report due to the present lack of knowledge about the potential safety of DINCH and to inform future studies. Besides, because imputing values below LOD using a single number may introduce bias for biomarkers with 30% under LOD (MEHP in this study), thus, we cautioned the interpretation for the association between MEHP and preterm birth (Lubin et al., 2004). All other phthalate biomarkers had detection rates higher than 90%. Second, we were unable to consider clinical subtypes of preterm birth (*e.g.*, spontaneous versus induced) due to the modest number of preterm births in this cohort. A previous study identified somewhat stronger associations between urinary phthalate metabolite concentrations and preterm birth among spontaneous preterm births compared with preterm births overall (Ferguson et al., 2019b). Third, residual confounding by socioeconomic factors or co-exposure to pollutant mixtures is possible. However, our findings were robust to adjustment for several potential confounders. Fourth, phthalates and DINCH are non-persistent chemicals with short half-lives and evaluating exposure in spot urine samples may lead to exposure misclassification. This would likely result in attenuation bias and a tendency towards null findings, rather than an overestimation of effects (Vernet et al., 2019). Finally, our findings may not be directly generalizable to fertile couples, as this study was conducted only among couples seeking treatment for infertility. It is possible that couples with infertility may be more susceptible to EDCs in the environment. However, it is likely that the underlying physiological mechanisms of the effects of phthalates on preterm birth would be consistent across fertile and subfertile populations. Future studies should evaluate potential effect modification of these relationships by infertility, which was beyond the scope of the present study. Another limitation is that this research was conducted within a cohort of mostly non-Hispanic white women. Future cohorts should enroll more diverse study populations to consider the potential impact of environmental exposures on racial and ethnic disparities in maternal health outcomes (James-Todd et al., 2016).

5. Conclusion

In this prospective study, maternal urinary concentrations of ∑DEHP metabolites during pregnancy were associated with an increased risk of preterm birth, and these associations were strongest during late gestation, which were in line with previous research findings. Although concerns about the safety of phthalates has resulted in replacement with chemicals such as DINCH, our findings suggest that exposure to DINCH may also affect reproductive and perinatal health, though caution is warranted when interpreting these findings given the small sample size. These results highlight a need for further research on these potential associations. These findings have considerable public health importance, given the ubiquitous exposure and the long-term implications of the outcome.

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.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.118476.

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Author statement

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