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A pilot investigation of couple-level phthalates exposure and *in vitro* fertilization (IVF) outcomes

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Abstract

Phthalates are reproductive toxicants in experimental animal studies and exposure has been associated with infertility in human populations, although the results have been inconsistent. To help to address the data gap, we conducted a hypothesis-generating investigation of associations between urinary phthalate metabolites and reproductive outcomes among women (n = 56) and their male partners (n = 43) undergoing *in vitro* fertilization (IVF). Urine was collected from participants on the day of oocyte retrieval. Samples were analyzed for a series of phthalates, MEP, MBP, MPP, MHxP, MEHP, MEHHP, MECPP, MiNP, MiDP, MCHP, and MBzP, using liquid chromatography-tandem mass spectrometry. We employed Poisson regression with robust variance estimation to estimate associations between urinary phthalate levels and biochemical pregnancy and live birth, adjusted for partner's concentration and confounding factors. Doublings in women's MBP (relative risk (RR) = 0.32, 95% CI: 0.13, 0.78), and men's MEHP (RR = 0.28, 95% CI: 0.09, 0.83), were associated with a lower likelihood for pregnancy. Doublings in women's (RR = 0.08, 95% CI: 0.01, 0.67) and men's (RR = 0.13, 95% CI: 0.02, 0.92) MHxP were associated with a lower likelihood of live birth. Our results suggest that phthalate exposure may impact IVF outcomes, and underscore the importance of including male partners when investigating the impact of phthalate exposure on IVF. These results also suggest that clinical recommendations

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Declaration of interests

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.

should include male partners for limiting phthalate exposure. Still, a larger and more comprehensive investigation is necessary to more definitively assess the risks.

Keywords

assisted reproduction; endocrine disruptors; female infertility; male infertility; phthalates; reproductive outcomes

1. Introduction

Phthalates are found in plastics, building materials, pharmaceuticals, and personal care products. Their nearly ubiquitous use in consumer goods has led to widespread human exposure [1, 2]. Experimental studies, *in vitro* and *in vivo*, have identified phthalates as endocrine-disrupting compounds that interfere with sex-steroid hormone activities, possibly having important implications for reproduction [3, 4]. Infertility, defined as the inability to conceive a pregnancy after 12 months of unprotected sexual intercourse, is a concern for approximately 9.4 million U.S. women [5]. The potential role of environmental pollutants, including phthalates, in the pathogenesis of infertility, is an increasing concern among clinicians and investigators worldwide [6, 7].

Phthalates are mixed into, rather than covalently bound to products, including plastics to impart flexibility, and are used as solvents and fragrance carriers in personal care products [8]. They can leach from plastics into the environment or foods and be absorbed and inhaled from personal care products, resulting in episodic, yet ongoing exposures [9, 10]. Food [11] and indoor dust inhalation [10] are primary sources of exposure to high molecular weight phthalates (HMW), such as di-2-ethylhexyl phthalate (DEHP), which are found in polyvinyl chloride (PVC) plastics. Exposure to low molecular weight phthalates (LMW), such as diethyl phthalate (DEP) and dibutyl phthalate (DBP), predominantly occurs from absorption or inhalation when using fragrances, lotions, and other personal care products [2, 8]. Ingestion of time-release capsules is another source of exposure to DBP, found in the enteric coating of some medications [2].

Several previous epidemiologic studies have estimated associations between phthalate exposures and reproductive outcomes, among populations conceiving with [12–17] and without assistance [18–22], although the results have been inconsistent. For example, a study of phthalate exposure among fertility compromised women using *in vitro* fertilization (IVF) found an inverse association between the sum of four urinary DEHP metabolites (ΣDEHP) and the probabilities of clinical pregnancy and live birth [15]. However, another study reported no statistically significant associations between urinary phthalate metabolites and pregnancy or live birth from IVF, although they found negative associations between urinary phthalate metabolites and numbers of total, mature, and fertilized oocytes [16]. Greater phthalates exposure, including DEHP, DBP, and DEP, has also been associated with poorer semen quality in general [23–26] and infertile populations [27–29], with potentially deleterious effects on fertility [13].

However, very few studies have assessed associations for female IVF patients and their male partners simultaneously [12, 13, 30]. This study adds data to the scant literature on the couple-based impacts of phthalate exposures on IVF outcomes, in a diverse U.S. population. In this hypothesis generating investigation, we examined associations between urinary phthalate metabolites and reproductive outcomes among couples using IVF, to help to guide the design of larger and more definitive future studies.

2. Methods

2.1 Sample selection and clinical protocol

Sixty-nine women and 56 male partners completing a first IVF cycle, using fresh non-donor oocytes and intending embryo transfer, were recruited at the University of California at San Francisco (UCSF) from 2015 to 2016. Patients received physical and gynecologic examinations and completed a fertility questionnaire to ascertain reproductive and medical histories. Following the baseline infertility evaluation, patients underwent gonadotropin-induced ovarian follicle stimulation per clinic protocols. Nearly two weeks later, when a sufficient number of follicles had developed to ≥ 17 mm diameter, human chorionic gonadotropin (hCG) was administered to trigger ovulation, and oocytes were retrieved within 36 hours. Women were advised to fast for at least eight hours to facilitate conscious sedation during oocyte retrieval. A fresh semen specimen was collected from the male partner on the same day as oocytes. Oocytes retrieved in metaphase-2 arrest were incubated (conventional IVF) or injected (intracytoplasmic sperm injection) with sperm and fertilization was confirmed by the appearance of 2 pronuclei approximately 24 hours later. Embryos were transferred 2–5 days later. Biochemical pregnancy (i.e., embryo implantation) was confirmed using a quantitative serum beta hCG ELISA test 14 days following the embryo transfer and women were contacted by mail nine months later to capture live birth.

Urine samples were collected from 56 female patients and 43 male partners on the day of oocyte retrieval and semen collection, prior to the procedure. Of the 56 female patients, 36 had male partners who elected to participate in this study, leaving 36 female-male couples. Spot urine specimens were collected in polypropylene urine cups and stored at −80 °C until transfer to the laboratory for analysis. We used an Atago “Pocket” handheld digital refractometer (Atago Co., LTD, Bellevue, WA USA) to measure urine specific gravity. The laboratory acid washed all consumables and samples from each lot were screened negative for phthalate contamination. The UCSF Committee on Human Research approved the study protocol. All participants completed informed consent at study enrollment.

2.2 Urinary phthalate metabolites analysis

Urine analysis was completed by the Clinical Toxicology and Environmental Biomonitoring Laboratory at UCSF, using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with an LC 1260-AB Sciex 5500 (Agilent, Santa. Clara, CA, USA), as previously described in detail [31]. Briefly, we quantified each detected analyte via an isotope dilution method, using a 10-point calibration curve (0.1–100 ng/mL). Observations below the limits of detection (LOD), 0.01 to 2.00 ng/mL, were included as directly measured from the instrument to limit bias in regression models; we did not impute values below the LOD

[32,33]. Eleven phthalate monoester metabolites were analyzed in urine, including monoethyl phthalate (MEP), a metabolite of DEP; monobutyl phthalate (MBP), a metabolite of DBP; mono-n-pentyl phthalate (MPP), a metabolite of di-n-pentyl-phthalate (DPP); mono-n-hexyl phthalate (MHxP), a metabolite of di-n-hexyl phthalate (DnHP); mono-2-ethylhexyl phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), metabolites of DEHP; mono-isononyl phthalate (MiNP), a metabolite of diisononyl phthalate (DiNP); mono-isodecyl phthalate (MiDP), a metabolite of diisodecyl phthalate (DiDP); monocyclohexyl phthalate (MCHP), a metabolite of dicyclohexyl phthalate (DCHP); and monobenzyl phthalate (MBzP), a metabolite of benzylbutyl phthalate (BzBP). We calculated ΣDEHP as the molar sum of MEHP, MEHHP, and MECPP; ΣLMW as the molar sum of MEP, MBP, and MPP; and ΣHMW as the molar sum of MHxP, MEHP, MEHHP, MECPP, MiNP, and MBzP. U.S. biomonitoring studies showed widespread exposure to these phthalate monoesters [1] and previous experimental studies have indicated their potential for reproductive toxicity [3, 4].

2.3 Statistical analysis

Distributions of all covariates and clinical factors were characterized. We examined urinary phthalate distributions and natural log-transformed the variables to normalize the distributions before analysis. The Wilcoxon signed-rank test was used to assess the paired differences in urinary phthalate metabolite concentrations between women and men. We assessed associations between urinary phthalates and covariates using Pearson correlation coefficients, Student's t-test, and ANOVA as appropriate.

In a first set of multivariable models, we used Poisson regression with robust variance estimation [34], to evaluate associations between pregnancy and live birth as outcomes, and individual urinary phthalate metabolite as predictors, adjusted for specific gravity as a covariate [35, 36]. We estimated the associations among female patients, male partners, and simultaneously among patients and partners (couples). In a second set of models, we further adjusted for confounding variables selected *a priori* as predictors of both phthalate exposure and IVF outcomes based on the literature, including: age in years [37], body mass index in kg/m^2 (BMI) (for women) [37,38], and "ever" vs. "never" history of cigarette smoking [39]. We employed multiple imputation with fully conditional specification to impute missing values for some covariates (12.5% of women and 9.3% of men) [40]. We examined model residuals to assess the adequacy of models.

We used principal component analysis (PCA) to characterize the mixture of urinary phthalate metabolites among couples (i.e., simultaneously including all phthalate metabolites measured in female patients and their male partners). We retained two factors to use as predictors of pregnancy and live birth, based on scree plots and eigenvalues >3.0 [41]. We retained Varimax rotated factor loadings that had correlations between individual phthalate metabolite concentrations and factors greater than |0.5| and corresponded to at least 10% of the total variability [42]. We multiplied each participant's factor value by the factor loading to emphasize those phthalates more closely related to the summary factor.

We set significance as α=0.05 for a 2-tailed test. We did not correct for multiple testing to increase sensitivity for detecting associations to be confirmed by a future investigation. We used SAS v.9.4 (SAS Institute Inc., Cary, NC, USA) for the statistical analysis.

3. Results

3.1 Distribution of demographics, clinical factors, and urinary phthalate metabolites among women and men

Table 1 describes the demographic and clinical factors for 56 women and 43 men undergoing IVF. Women were approximately 38 years old on average, and male partners were slightly older. Women's BMI ranged from 18.2 kg/m^2 to 38.6 kg/m^2 with an average of 24 kg/m^2. Approximately, 28.6% of women (n=16) and 23.3% of men (n=10) were Asian, with the remainder primarily white (i.e., n=26 women and n=19 men).

Table 2 describes the distribution of urinary phthalate metabolite concentrations among 56 women and 43 men. More than 97% of participants had urinary MEP, MBP, MHxP, MEHP, MEHHP, MECPP, and MBzP concentrations greater than the detection limits. We excluded MPP, MiNP, MiDP, and MCHP from further analysis as few values (<15%) were measured above the LODs. Supplemental Table 1 provides the specific gravity corrected urinary phthalate metabolite concentrations among 51 women and 40 men (n=5 women and n=3 men were missing specific gravity). Supplemental Table 2 examines correlations between individual and couple's urinary phthalate metabolites. HMW phthalate metabolites were moderately and positively correlated among women and among men. However, there were few significant correlations in urinary phthalate metabolites measured between women and men.

Supplemental Table 3 describes the associations between individual urinary phthalate metabolite concentrations and demographic and clinical factors. We detected statistically significant associations between greater age and lower urinary MEP and ΣLMW concentrations among men. We did not find significant differences in urinary phthalate metabolites according to race or cigarette smoking history. Similarly, there were no significant differences in urinary phthalate metabolites according to infertility diagnosis or treatment protocol.

3.2 Associations between individual urinary phthalate metabolite concentrations and IVF outcomes among women and men

Table 3 shows the results of the Poisson regression analysis between individual urinary phthalate metabolites in 56 women and 43 men, and IVF outcomes, adjusted for covariates. We found a pattern of mostly inverse associations between urinary phthalates and reproductive outcomes.

Women's MBP and men's MEHP concentrations were statistically significantly associated with a lower likelihood of pregnancy. In addition, women's urinary ΣLMW and MHxP were statistically significantly associated with a lower likelihood of live birth. Supplemental Table 4 shows the results adjusted only for urinary specific gravity.

3.3 Summary measures of couples' urinary phthalate metabolite concentrations

Supplemental Table 5 describes the results of our PCA among 56 women and 43 men. Factor 1 characterized the collective distribution of men's urinary phthalate concentrations, with all measured phthalate metabolites contributing to the loadings except MEP. Factor 2 did the same for women, but all measured phthalates contributed to the loadings, including MEP.

3.4 Associations between couples' urinary phthalate metabolite concentrations and IVF outcomes

Table 4 and Figure 1 show the results of the Poisson regression analysis between urinary phthalate metabolites and pregnancy for 36 couples, adjusted for partner's urinary phthalate concentration. We detected a significantly lower likelihood for pregnancy associated with doublings in women's MBP (relative risk (RR) = 0.32, 95% CI: 0.13, 0.78) and men's MEHP (RR = 0.28, 95% CI: 0.09, 0.83). Doublings in PCA Factor 1 (RR = 0.82, 95% CI: 0.64, 1.05), corresponding to men's overall urinary phthalates, and Factor 2 (RR = 0.76, 95% CI: 0.53, 1.09), corresponding to women's overall urinary phthalates, were also associated with a lower likelihood of pregnancy, albeit not statistically significant. Supplemental Table 6 shows the pregnancy results adjusted only for urinary specific gravity.

Table 4 and Figure 2 also describe associations for couples' (n=36) urinary phthalate metabolite concentrations with live birth, adjusted for partner's urinary phthalate concentration and other covariates. Doublings in women's urinary MBP concentration (RR = 0.16, 95% CI: 0.02, 1.19) and men's MEHP concentration (RR = 0.38, 95% CI: 0.10, 1.39) were associated with a lower likelihood of live birth, albeit not statistically significant. However, doublings in women's (RR = 0.08, 95% CI: 0.01, 0.67) and men's (RR = 0.13, 95% CI: 0.02, 0.92) urinary MHxP concentrations were statistically significantly associated with lower likelihoods of a live birth. Doublings in PCA Factors 1 (RR = 0.76, 95% CI: 0.56, 1.04) and 2 (RR = 0.72, 95% CI: 0.35, 1.49) were also associated with a lower likelihood of live birth, though neither was statistically significant. Supplemental Table 6 shows the live birth results adjusted only for urinary specific gravity.

4. Discussion

In this prospective pilot cohort study, we estimated associations between couples' urinary phthalates on the day of oocyte retrieval and IVF outcomes. We found that urinary MBP, MHxP, and MEHP, were associated with lower likelihoods of biochemical pregnancy and live birth when simultaneously considering exposure in the female patient and her male partner. We found a similar pattern of associations when estimating exposure only in women or only in men. In fact, using PCA, in a "mixtures-based" approach, we found that men's phthalate summary measures were similarly important as women's in associations with pregnancy and live birth. The results, concordant with previous studies reporting associations between phthalates and poorer sperm quality [17, 27, 29], underscore the importance of a "couples-based" approach to risk assessment.

4.1 Comparison to similar studies

Several groups previously reported on associations between urinary phthalates and reproductive outcomes among couples undergoing IVF [12–17]. In a large Saudi Arabian cohort (n=599) that measured eight urinary phthalates, higher concentrations of women's MEP and MEHP were associated with a probability of failed live birth after IVF, adjusted for male exposures [12]. In addition, this study also found that higher women's urinary MEP and MEHP were associated with a greater risk of a failed clinical pregnancy, when adjusted for men's concentrations. The geometric mean phthalate concentrations measured in that study were much higher than ours (e.g., women's MEP = 9137 ng/mL; women's MEHP = 388 ng/mL), possibly due to differences in exposure profiles attributed to country-specific lifestyles. Similar to their results, we also found that IVF couples with higher urinary MEHP concentrations were less likely to become pregnant. A smaller cohort from Wuhan, China (n=112), reported no association between eight follicular fluid or urinary phthalate metabolites, including MBP, MBzP, MEHHP, MEHP, and MEP, and IVF outcomes [14].

A long running Boston, Massachusetts study (n=218), measured 11 urinary phthalate metabolites and found inverse associations between male partners' urinary mono (3-carboxypropyl) phthalate (MCPP), mono carboxyoctyl phthalate (MCOP), and mono-isobutyl phthalate (MiBP) concentrations and embryo implantation after IVF, adjusted for female urinary phthalates [13]. The highest quartile of paternal urinary MCPP concentrations was associated with lower odds of a live birth (odds ratio (OR) = 0.42, 95% CI: 0.17, 1.07). While we did not measure MCPP, MCOP, or MiBP in our study, concordant with our findings, this study also reported lower odds for live birth in association with greater paternal urinary MBP concentrations. An additional analysis of women (n=256) from the same cohort, reported a greater risk of biochemical pregnancy loss for women in the highest relative to the lowest quartile of urinary ΣDEHP (i.e., MEHP, MEHHP, MEOHP, and MECPP) [17]. The authors speculated that some DEHP metabolites might associate with implantation, decidualization, placentation, or embryogenesis, possibly altering hormonal signaling and secretion of endogenous hormones such estrogen and progesterone. Another analysis of the women in this cohort reported associations between greater ΣDEHP and lower probabilities of clinical pregnancy and live birth [15]. We also found an inverse association between greater urinary ΣDEHP among women and pregnancy and live birth from IVF, although not statistically significant.

A study of 17 urinary phthalate metabolites measured in n = 136 Israeli IVF patients with a male factor or unexplained infertility diagnosis, reported associations between greater urinary ΣDEHP metabolites (i.e., MEHHP, MEOHP, and MECPP) and lower numbers of oocytes retrieved, mature oocytes, fertilized oocytes, and top-quality embryos [16]. Women in the highest quartile of ΣDEHP concentrations, had 2.9 fewer oocytes, 1.7 fewer mature oocytes, and 1.2 fewer fertilized oocytes on average than women in the lowest quartile, factors associated with poorer IVF outcomes. However, there was no association with pregnancy or live birth. Although inconsistent with our results, phthalate exposures were generally higher in that study, which had a larger sample size than our own.

Although conceiving without assistance, associations were reported for couples' pre-pregnancy urinary phthalates and pregnancy in a large prospective investigation of 14

urinary phthalate metabolites in couples [19]. In single partner models, men's urinary mono-methyl phthalate (MMP) (fecundability odds ratio (FOR) = 0.80, 95% CI: 70, 0.93), MBP (FOR = 0.82, 95% CI: 0.70. 0.97), and MBzP (FOR = 0.77, 95% CI: 0.65, 0.92) were associated with a longer time to conceive a pregnancy. In couples, greater men's urinary MMP (FOR = 0.81, 95% CI: 0.70, 0.94) and MBzP (FOR = 0.80, 95% CI 0.67, 0.97) concentrations were also associated with longer time to pregnancy. In contrast, our results did not indicate an association for men's urinary MBzP with pregnancy, adjusted for women's, and we did not measure MMP. Yet, we identified statistically significant inverse associations for women's and men's urinary MBP and MEHP with pregnancy, respectively. The discordant results might be related to higher MBzP in the previous study and higher MBP concentrations in our study. The different time windows for exposure (i.e., preconception in the previous study vs. completion of the 1st meiosis after administering the hCG trigger in the current study) and different study populations (i.e., unassisted conception in the previous study vs. assisted conception in the current study) may also be important. Still, the previous results reinforce our findings suggesting that the male's phthalate exposures may play an important role in pregnancy.

4.2 Study strengths and limitations

The results of this hypothesis-generating investigation have several limitations; therefore, our results should be interpreted with caution. The small sample size may have undermined our ability to detect modest associations and led to imprecise effect estimates in some regression models. Nevertheless, we retained sufficient statistical power to estimate joint associations between women's and men's urinary phthalates in single regression models adjusted for important confounding variables, and to identify hypotheses for future confirmation. We had few missing data points and our results were robust using a multiple imputation procedure to impute missing covariate information for some couples. Consistent with the exploratory nature of our study, to maximize detection of potential associations, we did not correct for multiple testing error [43]. Still, some associations may be chance findings given the large number of hypothesis tests and so our results require confirmation in a larger investigation.

Our reliance on a single spot urine sample may have misclassified phthalates exposure for some couples, given their short *in vivo* half-lives and substantial within-individual variabilities [44]. However, the habitual nature of exposure to LMW phthalates, such as DEP through use of personal care products, confers moderate reliability within-individual over time [12, 57], and previous studies report that a single spot urine sample is sufficient to describe average daily phthalate exposures [45]. Still, we expect that exposure misclassification was non-differential among women and so any bias was likely towards the null hypothesis. Furthermore, our fasting urine samples from women may have underestimated exposure to phthalates commonly associated with food products and food packaging materials, including metabolites of DEHP [46], which may also have underestimated associations among women. In fact, we detected very few values for MPP, MiNP, MiDP, and MCHP and we were unable to investigate them further. Nevertheless, we jointly modeled exposures from female patients and male partners in the same models, to more closely approximate the "couple-based" nature of reproduction.

We used PCA to generate “summary measures” for assessing associations between mixtures of phthalates, to more closely represent a real-life scenario [47]. The aforementioned Boston study also described associations between IVF outcomes and a mixture of eight urinary phthalate metabolites, bisphenol A, and parabens measured in women [28]. Women in the highest urinary DEHP metabolite concentration quartile had lower likelihoods of implantation (−22%), clinical pregnancy (−24%), and live birth (−38%) than women in the lowest quartile, although without statistical significance. A larger future investigation that uses a couples-based approach to more comprehensively integrate multiple phthalates in both partners will be necessary to interpret our results in a more definitive fashion.

Finally, we measured only urinary phthalate metabolites and so we cannot preclude confounding by other reproductive toxicants with similar sources of exposure, such as environmental phenols and parabens [48–50]. Similarly, we were unable to adjust for male BMI, a potentially important confounder when assessing IVF outcomes [51]. An E-value equal to 10.3 indicates that very strong unmeasured confounding could account for the observed association between men’s MHxP and live birth among couples in our study [52]. Although this was unlikely, a future paternal BMI-adjusted analysis is necessary to confirm the findings. We also did not adjust for socioeconomic status. However, couples initiating IVF treatment are often more educated and more affluent than the general population in U.S. states without mandated IVF treatment insurance coverage, like California [53–55]. Nevertheless, our study population is unlikely to represent all couples planning a pregnancy and may not be generalizable to infertile couples not using IVF [56].

5. Conclusions

Among couples undergoing infertility treatment, greater urinary phthalate metabolite concentrations were associated with lower likelihoods of pregnancy and live birth. In particular, exposures to MBP, MHxP, and MEHP were more strongly associated with pregnancy and live birth than other phthalate metabolites. Our results suggest that both female and male phthalate exposure may be similarly associated with IVF outcomes and so future investigations should consider couple-level exposure. Our results also suggest the importance of including the male partner in clinical recommendations for lifestyle and/or behavioral interventions with the aim to increase the chance of a live birth from IVF. However, given the exploratory nature of this study, these results will require confirmation in a larger and more comprehensive investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The study protocol was approved by the UCSF Committee for Human Research, and the Institutional Review Board at the University at Albany, State University of New York.

Abbreviations:

BBzP	benzylbutyl phthalate
BMI	body mass index
CI	confidence interval
DBP	dibutyl phthalate
DCHP	dicyclohexyl phthalate
DEHP	di-2-ethylhexyl phthalate
DEP	diethyl phthalate
DiDP	diisodecyl phthalate
DiNP	di-isononyl phthalate
DnHP	di-n-hexyl phthalate
DPP	di-n-pentyl-phthalate
FOR	fecundability odds ratio
hCG	human chorionic gonadotropin
HMW	high molecular weight
IVF	*in vitro* fertilization
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LMW	low molecular weight
LOD	limit of detection
MBP	monobutyl phthalate
MBzP	monobenzyl phthalate
MCHP	monocyclohexyl phthalate
MCOP	mono carboxyoctyl phthalate
MCPP	mono (3-carboxypropyl) phthalate
MECPP	mono-(2-ethyl-5-carboxypentyl) phthalate
MEHHP	mono(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	mono-ethylhexyl phthalate

MEP	monoethyl phthalate
MHxP	mono-n-hexyl phthalate
MiBP	mono-isobutyl phthalate
MiDP	mono-isodecyl phthalate
MiNP	mono-isononyl phthalate
MMP	mono-methyl phthalate
MPP	mono-n-pentyl phthalate
OR	odds ratio
PCA	principal component analysis
PVC	polyvinyl chloride
RR	relative risk
UCSF	University of California-San Francisco
ΣDEHP	molar sum of MEHP, MEHHP, and MECPP
ΣHMW	molar sum of MHxP, MEHP, MEHHP, MECPP, MiNP, and MBzP
ΣLMW	molar sum of MEP, MBP, and MPP

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Highlights:

- Urinary phthalate metabolites were measured in IVF patients and their male partners
- MBP, MEHP, and MHxP were inversely associated with biochemical pregnancy and live birth
- Associations for men were of similar importance as associations for women
- Clinical recommendations for interventions should consider both partners

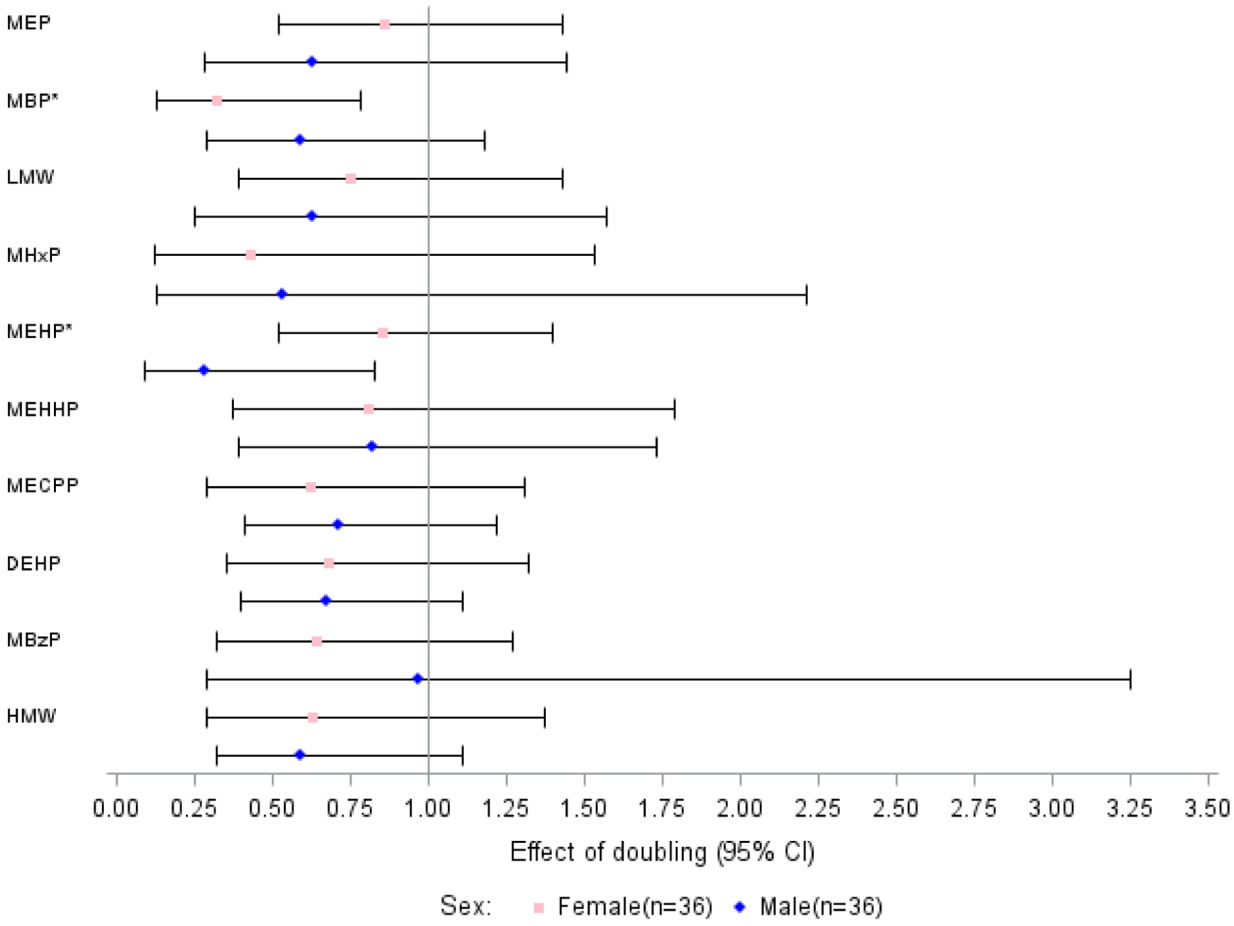

Figure 1.

Relative risks (95% confidence intervals) for an IVF pregnancy associated with a doubling in couples' urinary phthalate concentrations (ng/mL), adjusted for covariates (n=36)

NOTE: Adjusted for partners' ages (years), urinary specific gravities, histories of smoking ("ever" vs. "never"), women's body mass index (kg/m^2), and partner's urinary phthalates using individual Poisson models, and multiple imputation for participants with missing values for some covariates (n=2 women missing specific gravity, n=3 men missing specific gravity, n=1 missing BMI, n=1 man missing age).

* $p<0.05$.

Abbreviations: DEHP, di-2-ethylhexyl phthalate; HMW, high molecular weight phthalates; IVF, in vitro fertilization; LMW, low molecular weight phthalates; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEP, monoethyl phthalate; MHxP, monohexyl phthalate

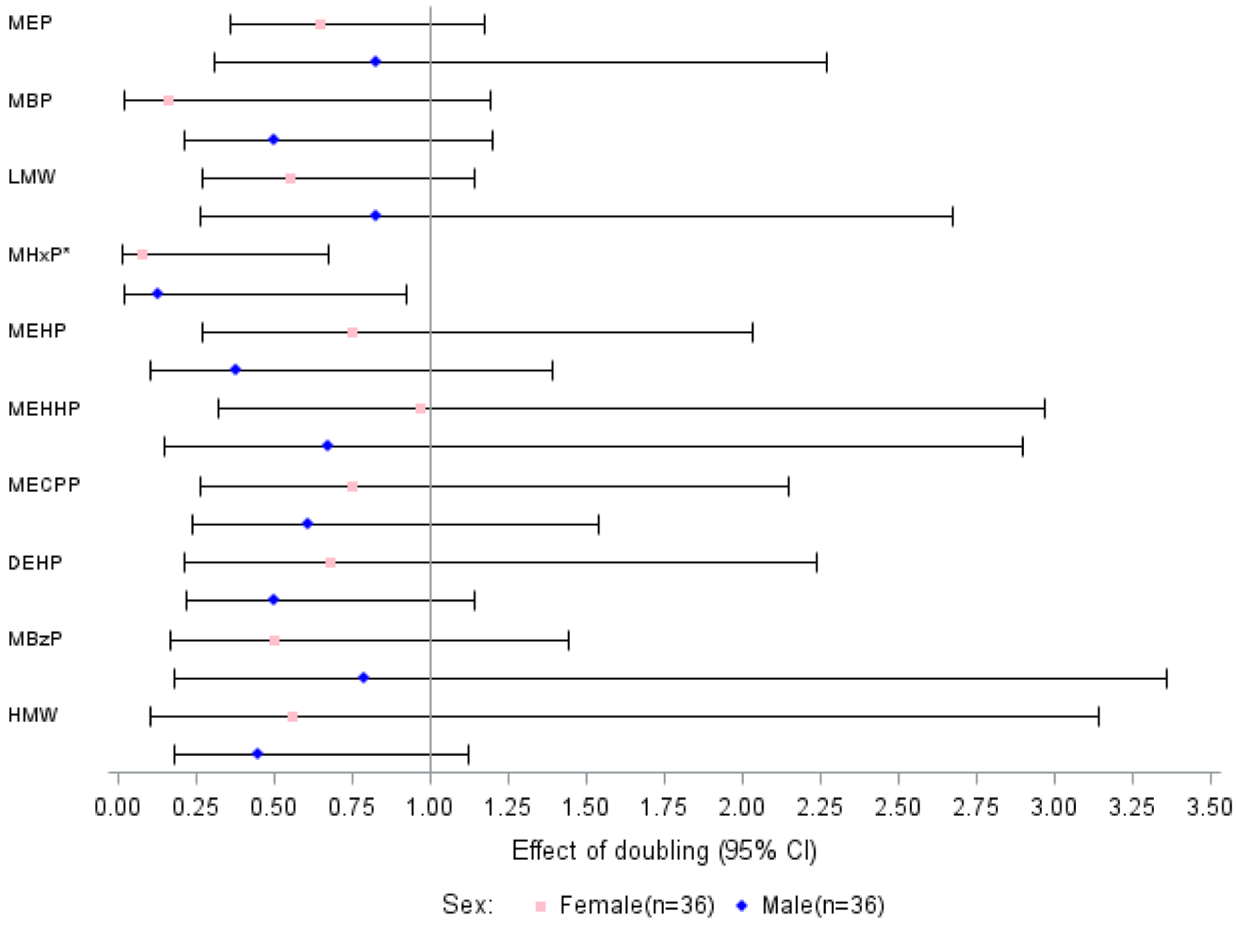

Figure 2.

Relative risks (95% confidence intervals) for an IVF live birth associated with a doubling in couples' urinary phthalate concentrations (ng/mL), adjusted for covariates (n=36)

NOTE: Adjusted for partners' ages (years), urinary specific gravities, histories of smoking ("ever" vs. "never"), women's body mass index (kg/m^2), and partner's urinary phthalates using individual Poisson models, and multiple imputation for participants with missing values for some covariates (n=2 women missing specific gravity, n=3 men missing specific gravity, n=1 missing BMI, n=1 man missing age).

* $p<0.05$.

Abbreviations: DEHP, di-2-ethylhexyl phthalate; HMW, high molecular weight phthalates; IVF, in vitro fertilization; LMW, low molecular weight phthalates; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEP, monoethyl phthalate; MHxP, monohexyl phthalate

Table 1.

Distribution of demographic and clinical factors among women (n=56) and men (n=43) undergoing IVF

Factors	Women	Men
Age, years (mean + SD)[a]	38.1 ± 3.34	39.6 ± 4.29
BMI (kg/m^2)[b]	24.0 ± 4.59	-
Race, n (%)		
Asian	16 (28.6)	10 (23.3)
Other	40 (71.4)	26 (60.5)
Missing	-	7 (16.3)
Ever smoking, n (%)		
Yes	11 (19.6)	1 (2.3)
No	45 (80.4)	42 (97.7)
Diagnosis, n (%)		
DOR	20 (35.7)	-
Unexplained	16 (28.6)	-
Male[c]	7 (12.5)	10 (23.3)
Tubal	5 (8.93)	-
Other	5 (8.93)	-
PCOS	3 (5.36)	-
Missing	-	1 (2.3)
Treatment, n (%)[d]		
Gonadotropin antagonist protocols	39 (69.6)	-
Lupron down-regulated protocols	12 (21.4)	-
Flare protocols	3 (5.36)	-
Missing	2 (3.57)	-
Outcomes, n (%)		
Pregnant	17 (30.4)	-
Live birth	12 (21.4)	-

[a] n=1 missing man;

[b] n=4 missing women;

[c] includes 7 couples without a primary female factor infertility diagnosis and 10 couples with a primary or secondary male factor infertility diagnosis;

[d] Gonadotropin antagonist protocols include IVF antagonist (n=21), IVF E_2-priming antagonist (n=14), NEP antagonist (n=3), and IVF antagonist-LP start (n=1); Lupron down-regulated protocols include IVF long luteal (n=2) and IVF demi-halt (no OCP) (n=10); Flare protocols include Aygestin priming CC flare antagonist (n=1), IVF Clomid flare-FSH/HMG (n=1), and Clomid only (n=1).

Abbreviations: BMI, body mass index; CC, Clomiphene Citrate; DOR, diminished ovarian reserve; E_2, estradiol; FSH, follicle stimulating hormone; HMG, human menopausal gonadotrophin; IVF, in vitro fertilization; LP, luteal phase; NEP, neutral endopeptidase; OCP, oral contraceptives; PCOS, polycystic ovary syndrome

Table 2.

Distribution of urinary phthalate metabolite concentrations (ng/mL) among women (n=56) and mean (n=43) undergoing IVF

Phthalate Metabolite	Geometric Mean	Geometric SD	Minimum	25th Percentile	50th Percentile	75th Percentile	Maximum	≥LOD (%)
MEP								
Women	30.0	3.66	1.44	10.8	29.5	72.6	971	100
Men	18.9	2.87	<LOD	8.96	15.7	42.2	601	98.0
MBP								
Women	16.1	2.82	<LOD	7.55	14.1	26.9	324	98.0
Men	9.72	2.59	1.75	4.97	7.59	17.0	252	100
ΣLMW[a]								
Women	258	3.19	18.4	120	240	511	5242	-
Men	155	2.82	13.5	83.2	125	330	3118	-
MPP								
Women	<LOD	1.05	<LOD	<LOD	<LOD	<LOD	0.36	5.0
Men	<LOD	1.14	<LOD	<LOD	<LOD	<LOD	1.15	9.0
MHxP								
Women	3.46	1.56	0.78	2.38	3.53	4.96	10.7	100
Men	2.05	1.64	0.35	1.26	1.76	3.46	10.0	100
MEHP								
Women	3.08	3.58	<LOD	0.66	2.03	3.50	114	98.0
Men	1.86	2.60	0.13	0.50	1.42	2.68	325	100
MEHHP								
Women	2.24	2.53	0.79	3.88	6.87	14.4	105	100
Men	6.17	2.78	0.69	2.56	4.30	9.64	315	100
MECPP *								
Women	19.5	2.94	2.39	8.35	16.4	46.5	373	100
Men	R.7	3.33	1.24	5.05	11.2	20.5	448	100
ΣDEHP[b] *								
Women	108	3.06	16.3	44.3	86.6	223	1895	98.0
Men	69.0	3.28	6.87	31.2	56.7	108	3673	100
MiNP								

Phthalate Metabolite	Geometric Mean	Geometric SD	Minimum	25th Percentile	50th Percentile	75th Percentile	Maximum	≥LOD (%)
Women	<LOD	1.69	<LOD	<LOD	<LOD	<LOD	10.5	9.0
Men	<LOD	1.68	<LOD	<LOD	<LOD	<LOD	5.13	14.0
MiDP								
Women	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	9.64	4.0
Men	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.0
MCHP								
Women	<LOD	1.06	<LOD	<LOD	<LOD	<LOD	0.54	2.0
Men	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	0.0
MBzP *								
Women	3.10	4.10	<LOD	0.99	2.31	5.61	52.3	98.0
Men	1.85	2.85	0.29	0.66	1.40	2.94	38.4	100
ΣHMW[c] *								
Women	148	2.72	24.3	67.3	131	365	1936	-
Men	89.5	3.01	13.2	40.5	74.7	143	3848	-

[a] ΣLMW (nmol/mL) as the molar sum of MEP, MBP, and MPP;

[b] ΣDEHP (nmol/mL) as the molar sum of MEHP, MEHHP, and MECPP;

[c] ΣHMW (nmol/mL) as the molar sum of MHxP, MEHP, MEHHP, MECPP, MiNP, and MBzP;

* $p<0.05$ for the difference between women and men using Wilcoxon signed rank test.

Abbreviations: IVF, in vitro fertilization; LOD, limit of detection; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MCHP, monocyclohexyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEP, monoethyl phthalate; MHxP, monohexyl phthalate; MiDP, mono-isodecyl phthalate; MiNP, mono-isononyl phthalate; MPP, mono-n-pentyl phthalate

Table 3.

Relative risks (95% confidence intervals) for IVF outcomes associated with a doubling in women's (n=56) and men's (n=43) individual urinary phthalate concentrations (ng/mL), adjusted for covariates

Phthalate Metabolite	Pregnant	p-value	Live Birth	p-value
MEP				
Women	0.83 (0.58, 1.19)	0.32	0.72 (0.48, 1.09)	0.12
Men	0.87 (0.53, 1.44)	0.59	1.09 (0.54, 2.20)	0.82
MBP				
Women	**0.65 (0.44, 0.97)**	**0.04**	0.61 (0.35, 1.05)	0.07
Men	0.77 (0.41, 1.46)	0.42	0.68 (0.25, 1.85)	0.45
ΣLMW				
Women	0.73 (0.49, 1.09)	0.13	**0.66 (0.44, 0.99)**	**0.04**
Men	0.82 (0.49, 1.37)	0.45	1.00 (0.46, 2.18)	0.99
MHxP				
Women	0.57 (0.19, 1.73)	0.32	**0.22 (0.05, 0.92)**	**0.04**
Men	0.80 (0.21, 3.08)	0.74	0.48 (0.07, 3.46)	0.46
MEHP				
Women	1.14 (0.85, 1.53)	0.37	0.99 (0.60, 1.63)	0.97
Men	**0.42 (0.19, 0.92)**	**0.03**	0.52 (0.20, 1.36)	0.18
MEHHP				
Women	1.15 (0.70, 1.90)	0.59	1.15 (0.55, 2.43)	0.71
Men	0.95 (0.61, 1.47)	0.81	0.70 (0.32, 1.55)	0.38
MECPP				
Women	0.98 (0.60, 1.60)	0.94	0.96 (0.49, 1.91)	0.92
Men	0.87 (0.56, 1.35)	0.53	0.60 (0.26, 1.38)	0.23
ΣDEHP				
Women	1.02 (0.66, 1.59)	0.91	0.95 (0.48, 1.87)	0.87
Men	0.82 (0.53, 1.29)	0.40	0.54 (0.21, 1.40)	0.20
MBzP				
Women	0.90 (0.61, 1.33)	0.59	0.93 (0.54, 1.63)	0.81
Men	1.32 (0.73, 2.40)	0.36	1.38 (0.61, 3.14)	0.44
ΣHMW				
Women	1.00 (0.61, 1.65)	0.99	0.88 (0.41, 1.90)	0.75
Men	0.82 (0.50, 1.35)	0.44	0.57 (0.22, 1.53)	0.26

NOTE: Adjusted for age (years),, urinary specific gravity, history of smoking ("ever" vs. "never") and body mass index (kg/m^2) in women using individual Poisson models, and multiple imputation for participants with missing values for some covariates (n=5 women missing specific gravity, n=3 men missing specific gravity, n=4 missing BMI, n=1 man missing age). P<0.05 in bold type.

Abbreviations: DEHP, di-2-ethylhexyl phthalate; HMW, high molecular weight phthalates; IVF, in vitro fertilization; LMW, low molecular weight phthalates; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEP, monoethyl phthalate; MHxP, monohexyl phthalate

Table 4.

Relative risks (95% confidence intervals) for IVF outcomes associated with a doubling in couples' individual or mixed urinary phthalate concentrations (ng/mL), adjusted for covariates and using multiple imputation for missing values (n=36)

Phthalate Metabolite	Pregnant	p-value	Live Birth	p-value
MEP				
Women	0.86 (0.52, 1.43)	0.56	0.65 (0.36, 1.17)	0.15
Men	0.63 (0.28, 1.44)	0.27	0.83 (0.31, 2.27)	0.72
MBP				
Women	**0.32 (0.13, 0.78)**	**0.01**	0.16 (0.02, 1.19)	0.07
Men	0.59 (0.29, 1.18)	0.13	0.50 (0.21, 1.20)	0.12
ΣLMW				
Women	0.75 (0.39, 1.43)	0.38	0.55 (0.27, 1.14)	0.11
Men	0.63 (0.25, 1.57)	0.32	0.83 (0.26, 2.67)	0.76
MHxP				
Women	0.43 (0.12, 1.53)	0.19	**0.08 (0.01, 0.67)**	**0.02**
Men	0.53 (0.13, 2.21)	0.38	**0.13 (0.0, 0.92)**	**0.04**
MEHP				
Women	0.85 (0.52, 1.40)	0.53	0.75 (0.27, 2.03)	0.57
Men	**0.28 (0.09, 0.83)**	**0.02**	0.38 (0.10, 1.39)	0.15
MEHHP				
Women	0.81 (0.37, 1.79)	0.60	0.97 (0.32, 2.97)	0.95
Men	0.82 (0.39, 1.73)	0.60	0.67 (0.15, 2.90)	0.59
MECPP				
Women	0.62 (0.29, 1.31)	0.21	0.75 (0.26, 2.15)	0.59
Men	0.71 (0.41, 1.22)	0.22	0.61 (0.24, 1.54)	0.30
ΣDEHP				
Women	0.68 (0.35, 1.32)	0.26	0.68 (0.21, 2.24)	0.53
Men	0.67 (0.40, 1.11)	0.12	0.50 (0.22, 1.14)	0.10
MBzP				
Women	0.64 (0.32, 1.27)	0.20	0.50 (0.17, 1.44)	0.20
Men	0.97 (0.29, 3.25)	0.97	0.79 (0.18, 3.36)	0.75
ΣHMW				
Women	0.63 (0.29, 1.37)	0.24	0.56 (0.10, 3.14)	0.51
Men	0.59 (0.32, 1.11)	0.10	0.45 (0.18, 1.12)	0.09
PCA				
Factor 1[a]	0.82 (0.64, 1.05)	0.11	0.76 (0.56, 1.04)	0.09
Factor 2[b]	0.76 (0.53, 1.09)	0.14	0.72 (0.35, 1.49)	0.38

NOTE: Adjusted for partners' ages (years), urinary specific gravities, histories of smoking ("ever" vs. "never"), women's body mass index (kg/m^2), and partner's urinary phthalates using individual Poisson models, and multiple imputation for participants with missing values for some covariates (n=2 women missing specific gravity, n=3 men missing specific gravity, n=1 missing BMI, n=1 man missing age). P<0.05 in bold type.

[a]Factor 1 describes men with higher urinary MBP, MHxP, MEHP, MEHHP, MECPP, and MBzP concentrations;

[b] Factor 2 describes women with higher urinary MEP, MBP, MHxP, MEHP, MEHHP, MECPP, and MBzP concentrations.

Abbreviations: DEHP, di-2-ethylhexyl phthalate; HMW, high molecular weight phthalates; IVF, in vitro fertilization; LMW, low molecular weight phthalates; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEP, monoethyl phthalate; MHxP, monohexyl phthalate; PCA, principal component analysis