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Association of urinary phthalate (UrP) metabolite concentrations with ovarian response and early in-vitro fertilization (IVF) outcomes

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Study question

In women undergoing in-vitro fertilization (**IVF**), is there an association between UrP and ovarian response, oocyte yield, embryonic development and/or implantation failure (**IF**)?

Summary answer

Increased UrP were associated with decreased yield of retrieved and mature oocytes and increased odds for implantation failure.

What is known already

In experimental studies, some phthalate (**P**) metabolites alter endocrine signaling pathways in the rodent ovary. Limited occupational studies link phthalate exposure with adverse reproductive outcomes. Despite widespread human exposure to phthalates, little is known about the effects of low-level, daily exposures to phthalates on ovarian function and hence on women's reproductive health.

Study design, size, duration

Prospective cohort; 231 women (18-45 years old) undergoing 325 fresh IVF cycles at the Massachusetts General Hospital Fertility Center in Boston, MA, USA. Between 11/2004 and 03/2012, 598 urine samples were collected either at the early/mid-follicular phase and/or at oocyte retrieval.

Participants/materials, setting, methods

UrP measured: *mono(2-ethylhexyl)-P* (**MEHP**), *mono(2-ethyl-5-hydroxyhexyl)-P*, *mono(2-ethyl-5-oxohexyl)-P*, *mono(2-ethyl-5-carboxylpentyl)-P*, *monobenzyl-P*, *monoethyl-P*, and *monobutyl-P* (**MBP**). The molar sum of *di-2-ethylhexyl-P* (**sum-DEHP**) metabolites was calculated
Statistics: Mixed effects and Poisson regression models adjusted for potential confounders.
Outcome measures: Serum peak estradiol, number of retrieved, mature, and fertilized oocytes, embryonic cleavage and implantation failure.

Main results and the role of chance

Most UrP were detected in >95% of urine samples. The odds for IF increased with increasing quartiles of i) sum-DEHP metabolites [Odds Ratios (**OR**s) for quartiles Q2, Q3, and Q4 vs Q1: 1.41, 1.76, 2.05, respectively, *p*-trend=0.031], and ii) MBP (ORs: 1.96, 2.02, 1.85, respectively, *p*-trend=0.087). There was a 4.17% (Q2), 6.19% (Q3), and 11.4% (Q4) decrease in the number of retrieved oocytes with increasing MEHP quartiles (as compared to Q1, *p*-trend=0.052), and a similar 9.09%, 9.46%, 10.2% decrease with increasing quartiles of sum-DHEP metabolites (*p*-trend =0.074). There was a decrease in the number of

mature oocytes with increasing MEHP quartiles (range: 3.03%-14.8%, *p*-trend=0.016), and sum-DEHP metabolites (range: 11.9%-14.4%, *p*-trend=0.018). There were no associations of UrP with peak estradiol, rates of fertilization or embryonic cleavage.

Limitations, reason for caution
UrP were measured in urine samples collected during the IVF cycle and reflect only short-term exposure. Measured urinary concentrations might not accurately represent long-term exposure and its contribution to the observed early IVF outcomes. Results may not be generalizable to women conceiving naturally.

Wider implications of the findings
MEHP and sum-DEHP metabolites were associated with lower oocyte yield and the latter was also associated with increased odds of implantation failure in IVF. Our data support the hypothesis that exposure to specific phthalates might lead to adverse female reproductive outcomes.

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Trial registration number
None