Urinary phthalate metabolite concentrations in relation to history of infertility and use of assisted reproductive technology

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Objective: To examine urinary phthalate metabolite concentrations in pregnant women with planned pregnancies in relation to history of infertility and use of assisted reproductive technology (ART).
Design: Phthalate metabolite concentrations were measured in first-trimester urine samples collected from women participating in a prospective pregnancy cohort study.
Setting: Prenatal clinics.
Patient(s): A total of 750 women, of whom 86 had a history of infertility. Forty-one women used ART to conceive.
Intervention(s): None.
Main Outcome Measure(s): Primary outcomes were concentrations of four metabolites of diethylhexyl phthalate (DEHP) and their molar sum (∑DEHP). Multivariable analyses compared phthalate metabolite levels in [1] women reporting a history of infertility vs. those who did not (comparison group); and [2] those who used ART to conceive the index pregnancy vs. women with a history of infertility who did not use ART.
Result(s): Among women with a history of infertility, ∑DEHP was significantly lower in women who conceived after ART compared with those who did not (geometric mean ratio: 0.83; 95% confidence interval 0.71–0.98). Similar significant associations were observed for all of the individual DEHP metabolites. There were no differences in DEHP metabolite concentrations between women with a history of infertility and the comparison group.
Conclusion(s): Women who used ART to conceive had lower first-trimester phthalate metabolite concentrations than women with a history of infertility who did not use ART. Further research is needed to explore whether those pursuing fertility treatments take precautions to avoid exposure to environmental toxins, to improve treatment outcomes. (Fertil Steril® 2015;104:1227–35. ©2015 by American Society for Reproductive Medicine.)
Key Words: Phthalate, infertility, ART, endocrine-disrupting chemicals (EDCs)

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In 2000, 50–80 million people worldwide experienced some form of infertility, defined as failure to achieve clinical pregnancy after 12 consecutive months of unprotected intercourse (1). In the United States, this number is expected to increase from 4 million in the early 1980s to 5.4–7.7 million by the year 2025, highlighting the importance of understanding factors contributing to this rise (2).

Paralleling this increase in infertility, there has been a sharp rise in the production of synthetic chemicals, many of which may have endocrine-disrupting properties (3). As a result, there has been concern as to whether endocrine-disrupting chemicals (EDCs) may impact human fertility (4, 5). Numerous EDCs, including DDT (dichlorodiphenyltrichloroethane), BPA (bisphenol A), and TCDD (2,3,7,8-tetrachlorodibenzodioxin), have now been linked to changes in ovarian function, longer time to pregnancy, and increased risk of early pregnancy loss (6–10). Although the mechanisms remain uncertain, EDCs may impact fertility by disrupting the hypothalamic–pituitary axis or by altering hormone synthesis and transport (11–14). In 2013 the American College of Obstetrics and Gynecology and the American Society for Reproductive Medicine issued a joint committee opinion on the health impact of EDCs, underscoring the clinical relevance of better understanding these exposures. The statement emphasized how toxic environmental agents can have a profound effect on reproductive health and encouraged clinicians to educate patients on EDCs and how they might reduce their exposure (15).

Among the chemicals highlighted in the report are phthalates, a class of EDCs widely used in the manufacture of industrial goods, pharmaceuticals, personal care products, and foodstuffs (16). In the 2011–2012 cycle of the National Health and Nutrition Examination Survey (NHANES), 9 of the 13 urinary phthalate metabolites measured were detectable in more than 99% of individuals (17). Phthalates have been linked to numerous adverse health outcomes in human and animal models (18–23). Of the phthalates studied thus far, di-2-ethylhexyl phthalate (DEHP) and its metabolites have attracted the most concern owing to their antiandrogenic properties. In female animal models DEHP exposure is associated with decreased concentrations of key reproductive hormones, such as E_2 (24, 25). Prenatal exposure to DEHP (and selected other phthalates) is linked to a spectrum of genital abnormalities in male rodents (termed the "phthalate syndrome"), including cryptorchidism, altered anogenital distance, and decreased sperm counts (26). In humans, prenatal phthalate exposure is similarly linked to altered male reproductive development and changes in sex-specific childhood behavior (27, 28). Phthalate exposure in adulthood has been associated with reduced semen quality and sex hormone concentrations (18, 29). Despite intense interest in phthalate exposure and reproductive health in men, little is known about phthalates in relation to women's fertility. Given that T and E_2 play integral roles in female reproductive capacity, and concentrations of both hormones seem to be altered by phthalate exposure, this question merits further attention.

Several studies have examined phthalate exposure in relation to female reproductive outcomes; however, few have explicitly focused on fertility (30). In female mice, exposure to DEHP and its metabolite mono-2-ethylhexyl phthalate (MEHP) are associated with lower rates of live birth (31). One possible mechanism is that phthalates may impair ovarian and follicular function, which consequently can interfere with conception. Supporting this possibility, in female rats DEHP exposure is associated with lower E_2 concentrations and lower rates of ovulation (24, 32). Similarly, MEHP induces ovarian toxicity in rodent ovarian follicles through suppression of follicular development (33).

Few epidemiologic studies have specifically examined women's fecundity in relation to phthalate exposure. In one study, occupational phthalate exposure was associated with impaired female fecundity; however, information on phthalate levels was inferred on the basis of occupation rather than directly quantified (34). A prospective pregnancy cohort study found that urinary levels of mono-methyl phthalate, mono-butyl phthalate (MBP), and mono-benzyl phthalate were inversely associated with male, but not female, fecundity. However, phthalate concentrations were lower than those reported elsewhere (including in NHANES), and by excluding anyone with diagnosed infertility, they may have removed the population of greatest concern (35). A third pregnancy cohort study found nonsignificant associations between first-trimester phthalate exposure and shorter time to pregnancy, but also excluded infertile women (36).

Distinguishing between couples who conceive with assisted reproductive technology (ART) vs. those who do not is relevant because [1] couples requiring ART may represent a population with more severely impacted fertility; and [2] couples who undergo ART receive more medical procedures, which presents additional opportunities for phthalate exposure through medical supplies and pharmaceuticals.

In this study we examined whether phthalate concentrations were associated with either women's history of infertility or use of ART. We used data from a large, multicenter pregnancy cohort study to examine concentrations in [1] women with a history of infertility compared with women with no history of infertility; and [2] women who used ART to conceive the index pregnancy compared with infertile women who conceived without ART. Because of the well-documented differences between planned and unplanned pregnancies, we limited the present analyses to planned pregnancies (37–39). This work adds to the limited literature on phthalates in relation to women's infertility and is the first to examine phthalates in relation to infertility and use of ART.

MATERIALS AND METHODS

Overview of Recruitment

The Infant Development and Environment Study (TIDES) is a multicenter cohort study designed to examine the association between maternal phthalate exposures and infant health and development. Between 2010 and 2012, pregnant women aged 18 and older were recruited through prenatal care clinics at four academic medical centers across the United States: University of Minnesota, University of Rochester, Seattle Children's Hospital or University of Washington School of Medicine, and University of California at San Francisco (UCSF). Eligibility criteria included the following: less than 13 weeks pregnant, English-speaking (or Spanish-speaking at the California center), planning to deliver at a study hospital, and no serious medical conditions (particularly psychiatric conditions that would make them poor candidates for longitudinal follow-up) or threats to the pregnancy (whereby a first-trimester loss seemed probable). The institutional