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Environmental exposure to di-2-ethylhexyl phthalate is associated with low interest in sexual activity in premenopausal women

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ABSTRACT

Phthalates, a ubiquitous class of environmental chemicals, may interfere with typical reproductive hormone production both *in utero* and in adulthood. Although they are best known as anti-androgens, increasingly, evidence suggests that phthalates, particularly di-2-ethylhexyl phthalate (DEHP), may also suppress estrogen production. Given that both androgens and estrogens are essential for sexual function, particularly sexual interest, it is plausible that adult exposure to phthalates alters sexual function. To this end, we used data from 360 women participating in a pregnancy cohort study (the Study for Future Families) to examine whether urinary phthalate metabolite concentrations were associated with two dimensions of self-reported sexual dysfunction in the months prior to conception: lack of sexual interest and vaginal dryness. Women in the highest quartile of urinary concentrations of mono-2-ethyl-5-hydroxyhexyl phthalate, a DEHP metabolite, had 2.58 (95% CI 1.33, 5.00) times the adjusted odds of reporting that they almost always or often lacked interest in sexual activity, and results were similar for mono-2-ethyl-5-oxohexyl phthalate (aOR: 2.56, 95% CI 1.32, 4.95), another DEHP metabolite. Self-reported vaginal dryness was not associated with any phthalate metabolite concentration. This study is novel in its focus on sexual function in relation to environmentally relevant (rather than occupational) exposure to phthalates in adult women and these preliminary findings merit replication in a large, prospective study. Better understanding how adult exposure to phthalates may affect reproductive health, including sexual function, is of public health interest given that virtually all Westerners are exposed to phthalates.

Introduction

In humans and other primates, reproductive hormones are essential drivers of sexual motivation and interest; in the absence of androgens, sexual interest decreases sharply (Dixson, 1993; Kwan et al., 1983; Resko and Phoenix, 1972; Schenck and Slob, 1986; Wallen, 2001). In hypogonadal men, testosterone administration elicits increased sexual arousal and enjoyment (O'Connor et al., 2004; Skakkebaek et al., 1981; Wang et al., 2004) whereas experimentally-induced hypogonadism reduces sexual function (which can then be restored by testosterone administration) (Schmidt et al., 2009). More recent work on hypogonadism suggests that not only is testosterone important, but estradiol also contributes to the restoration of sexual function in men (Finkelstein et al., 2013). In females, the hormonal correlates of sexual interest have been more complicated to unravel. The dramatic changes in reproductive hormone concentrations across the menstrual cycle make it difficult to determine the precise role that individual hormones play in sexual interest; however, the precipitous drop in sexual interest in ovariectomized women (and its restoration with combined estradiol and testosterone therapy) demonstrates the central role of sex steroid hormones in female sexual motivation (Sherwin and Gelfand, 1987; Sherwin et al., 1985).

Despite the preponderance of evidence demonstrating that reproductive hormones are essential for sexual interest and motivation, there has been very little research on the extent to which exposure to

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endocrine-disrupting chemicals (EDCs) in adulthood may affect sexual interest and behavior in humans and other primates. EDCs can act through multiple mechanisms including mimicking endogenous hormones or blocking hormone production. Of particular relevance to sexual function are EDCs that alter reproductive hormone concentrations. Evidence from numerous animal species shows that EDC exposure (experimental or environmental) can exert widespread effects on sexual behavior, impairing species- and sex-typical proceptive and receptive behaviors (reviewed in Blocker and Ophir, 2013).

Exposure to synthetic EDCs in the modern world is ubiquitous (Woodruff et al., 2011), nevertheless, there has been little research on EDCs and sexual function in humans, and most of it focuses on supra-normal exposures in men. Loss of male sexual interest and motivation has been linked to high exposure to insecticides and delousing agents believed to be EDCs (Brody and Loriaux, 2003; Munk and Nantel, 1977; Sonnenschein and Soto, 1998). Similarly male workers occupationally exposed to bisphenol A (BPA), a weakly estrogenic EDC, reported lower sexual desire and, more generally, greater sexual dysfunction, than controls (Li et al., 2010a, 2010b). To our knowledge only one study has reported on sexual function in relation to environmentally relevant levels of EDC exposure, finding that urinary BPA concentrations were inversely associated with level of self-reported sex drive and ejaculation strength (Li et al., 2010b). Additional research on the relationship between exposure to environmentally-relevant concentrations of EDCs and sexual function is needed, as is work on whether EDCs affect sexual function in women, a heretofore unstudied question (Lara et al., 2012).

Phthalates are a class of EDCs that may be particularly relevant in this context. They are used in the production of a wide range of consumer products including foodstuffs, personal care products, pharmaceuticals, vinyl flooring, electronics, and pesticides. Exposure is virtually ubiquitous in Western populations (Koch and Calafat, 2009; Woodruff et al., 2011) and phthalates' anti-androgenic properties have been widely documented (Foster, 2006; Gray et al., 2000; Swan et al., 2005). In adult men and peripubertal boys, phthalate metabolite concentrations are inversely associated with serum free testosterone concentrations and the free androgen index as well as estradiol concentrations (Duty et al., 2005; Ferguson et al., 2014; Meeker et al., 2009; Meeker and Ferguson, 2014; Mendiola et al., 2012; Pan et al., 2006). Little is known about how phthalate exposure affects hormone activity in women. We found that in pregnant women, urinary concentrations of metabolites of several phthalates (including di-2-ethylhexyl phthalate (DEHP)) were associated with lower testosterone and estradiol concentrations (Sathyanarayana et al., 2014) and more recently, in the National Health and Nutrition Examination Survey (NHANES), associations were found between certain phthalate metabolites and testosterone levels in women, particularly among the 40–60 year old age group (Meeker and Ferguson, 2014). Evidence from animal models echoes these results and suggests that certain phthalates, such as DEHP, are not only anti-androgenic, but may alter activity of other hormones including estradiol, progesterone, and thyroid hormones (Davis et al., 1994; Harris et al., 1997; Huang et al., 2007; Jobling et al., 1995; Lovekamp and Davis, 2001; Meeker et al., 2007; Meeker and Ferguson, 2011; Treinen et al., 1990).

Given these multiple lines of evidence suggesting that adult exposure to phthalates may alter typical reproductive hormone activity in humans, we used data from a large pregnancy cohort study to explore the extent to which phthalate exposure is also related to sexual function. Our primary analyses examine the relationship between phthalate exposure and self-reported a lack of interest in sexual activity in adult women, and we hypothesize that urinary concentrations of phthalate metabolites (particularly DEHP metabolites) are inversely associated with self-reported interest in sexual activity. Secondarily, we examine whether phthalate metabolite concentrations are associated with a second aspect of women's sexual dysfunction, vaginal dryness.

Methods

Study population

Pregnant women and their partners were recruited into the Study for Future Families (SFF) from four cities around the United States (Los Angeles, CA, Minneapolis, MN, Columbia, MO, and Iowa City, IA) from 1999–2002. To be eligible, couples had to be age 18 or older, have a non-medically assisted pregnancy, have no major threat to the pregnancy, be receiving prenatal care at one of the participating obstetric clinics, and speak English or Spanish. Subjects completed questionnaires and a subset gave blood and urine samples during the same visit. Eligibility for inclusion in the current analyses included having completed a questionnaire and given a urine sample which was analyzed for phthalate metabolites. Human subject committees at the participating institutions approved the study and all subjects signed informed consent prior to participating in any study activities.

Questionnaires

During the pregnancy, subjects completed an extensive questionnaire including items on demographics, lifestyle, and reproductive history. They were asked a short series of questions on sexual health. In particular, they were asked the question "In the three months before your current pregnancy, how often did you have difficulty with the following?" and then were given items on "lack of interest in sex" and "vaginal dryness". For each item, subjects chose from the following possible responses: almost always, often, sometimes and almost never. In addition, the questionnaire included items on age, race and ethnicity, parity, educational attainment, medication use, and stress, among other things. Stress was assessed through a set of items on stressful life events (SLEs) occurring in the previous three months. Items were derived from two widely-used questionnaires (Dohrenwend et al., 1978; Holmes and Rahe, 1967), and included: job loss or unemployment (self or partner); serious injury or illness (self or partner); death of a close family member (*i.e.* parent, child, sibling); divorce, separation, or serious relationship difficulties with one's partner; serious legal or financial problems (self or partner); or other major life events (write-in option) (Barrett et al., 2013).

Phthalate metabolite measurements

All subjects collected urine in polypropylene cups, after which the urine was aliquoted and frozen at −80 °C. Samples from subjects who continued to participate in the study postnatally (n = 380) were subsequently analyzed for urinary phthalate metabolite concentrations at the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, which had no access to subjects' data or identifiers. The samples were analyzed according to a modification of a previously published method (Silva et al., 2004). In short, the assays entailed enzymatic hydrolysis of phthalate metabolites from their conjugated form, followed by automated on-line solid-phase extraction, separation with high-performance liquid chromatography, and detection by isotope-dilution tandem mass spectrometry (Silva et al., 2004). Nine phthalate metabolites were quantified simultaneously: monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), monomethyl phthalate (MMP), monobenzyl phthalate (MBzP), monoisobutyl phthalate (MiBP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), and mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP). Limits of detection (LODs) were in the low nanogram per milliliter range. To improve precision and accuracy, isotopically labeled internal standards and conjugated internal standards were used. Between-day relative standard deviations were less than 10% and quality control samples and laboratory blanks were used to assess performance. At the time of phthalate metabolite measurements,