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Maternal and paternal serum concentrations of persistent organic pollutants and the secondary sex ratio: A population-based preconception cohort study

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ABSTRACT

Recent declines in the secondary sex ratio (SSR), defined as the ratio of males to females at birth, in some industrialized countries may be attributed to exposure to environmental toxicants such as persistent organic pollutants (POPs). This study aimed to evaluate the association of couples' preconception exposure to POPs with the SSR. The study cohort comprised 235 couples who were enrolled in the Longitudinal Investigation of Fertility and the Environment (LIFE) Study between 2005 and 2009 prior to conception and prospectively followed through delivery of a singleton birth. Upon enrollment, couples' serum concentrations (ng/g) were measured for 9 organochlorine pesticides, 1 polybrominated biphenyl, 10 polybrominated diphenyl ethers, and 36 polychlorinated biphenyls (PCBs). Birth outcome data including infant sex were collected upon delivery. Modified Poisson regression models were used to estimate the relative risks (RRs) and 95% confidence intervals (CIs) of a male birth for each chemical. Of the 56 POPs examined, maternal PCB 128 and paternal hexachlorobenzene were significantly associated with a female excess (RRs, 0.75 [95% CI, 0.60–0.94] and 0.81 [95% CI, 0.68–0.97] per 1 SD increase in log-transformed serum chemical concentrations, respectively), whereas maternal mirex and paternal PCB 128 and p,p′-dichlorodiphenyldichloroethylene were significantly associated with a male excess (RR range, 1.10–1.22 per 1 SD increase in log-transformed serum chemical concentrations). After adjusting for multiple comparisons, only maternal mirex remained significantly associated with the SSR. This exploratory study on multiple classes of POPs demonstrated no conclusive evidence on the association between parental preconception exposure to POPs and the SSR.

1. Introduction

The secondary sex ratio (SSR) is the ratio of males to females at birth, while the primary sex ratio is the ratio at conception (Buck Louis and Platt, 2011). Across multiple academic disciplines including demography, sociobiology, epidemiology, and environmental science, the SSR has long been the subject of scientific investigation, serving as a useful tool in monitoring population dynamics and health (McDonald et al., 2014). The stability and variability of the SSR observed at the population level have been proposed to be influenced by a variety of endogenous and exogenous factors, such as parental ages (Chahnazarian 1988; Jacobsen et al., 1999; Mathews and Hamilton, 2005), birth order (Biggar et al., 1999; Mathews and Hamilton, 2005), race/ethnicity (Davis et al., 2007; Mathews and Hamilton, 2005), follicular phase length (Martin, 1997; Weinberg et al., 1995), timing of conception within the menstrual cycle (Martin, 1997; James, 2008b), stress (Bae et al., 2017b; Fukuda et al., 1998; Zorn et al., 2002), endocrine and immunological effects (James, 2008a; Ober, 1992), and other environmental factors (Terrell et al., 2011). In particular, there has been speculation that recent declines in the SSR in some developed countries may be attributed to ubiquitous exposure to environmental toxicants (Davis et al., 2007; Grech et al., 2003; Mathews and Hamilton,

Abbreviations: CI, confidence interval; DBCP, dibromochloropropane; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; FSH, follicle-stimulating hormone; GED, General Educational Development; GM, geometric mean; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; LH, luteinizing hormone; LIFE, Longitudinal Investigation of Fertility and the Environment; LOD, limit of detection; NHANES, National Health and Nutrition Examination Survey; OCP, organochlorine pesticide; OR, odds ratio; PBB, polybrominated biphenyl; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PFAS, perfluoroalkyl and polyfluoroalkyl substance; POP, persistent organic pollutant; RR, relative risk; SD, standard deviation; SSR, secondary sex ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin

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2005). Indeed, the decreasing trends in the SSR are juxtaposed with other adverse trends in reproductive outcomes, such as testicular cancer, genitourinary malformations, fecundity impairments, and gynecologic disorders (Buck Louis et al., 2011a; Skakkebaek et al., 2001). Of late, these phenomena have been synthesized in the paradigms of the testicular dysgenesis syndrome in males (Skakkebaek et al., 2001) and the ovarian dysgenesis syndrome in females (Buck Louis et al., 2011a), providing conceptual frameworks for assessing environmental influences on human reproduction.

Persistent organic pollutants (POPs) are of major public health concern, given their long half-lives and tendency to bioaccumulate and biomagnify in wildlife and humans. Exposure to POPs, such as dioxins, organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and polybrominated diphenyl ethers (PBDEs), particularly during the sensitive windows of human reproduction has been investigated in relation to a variety of reproductive outcomes, given the purported endocrine-disrupting properties of these chemicals (Nicolopoulou-Stamati and Pitsos, 2001; Toft et al., 2004; Vested et al., 2014). Along with considerable experimental evidence suggesting the harmful effects of POPs on reproduction in terms of oocyte maturation and follicle physiology (Bhattacharya and Keating, 2012; Pocar et al., 2003), a growing body of epidemiologic evidence has demonstrated that exposure to POPs may adversely affect human reproduction, possibly influencing reproductive hormones, menstrual cycles, semen quality, and couple fecundity among others (Buck Louis et al., 2013, 2016; Mumford et al., 2015; Nicolopoulou-Stamati and Pitsos, 2001; Toft et al., 2004; Vested et al., 2014).

Previous reports have suggested that parental exposure to POPs may be associated with alterations in the SSR. For instance, in landmark studies among the resident population in Seveso, Italy following a chemical manufacturing plant explosion in 1976, paternal exposure to high levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) was found to be associated with the reversal of the SSR (i.e., an excess of female births) (Mocarelli et al., 1996, 2000). Several studies have also investigated PCBs in relation to the SSR, demonstrating equivocal findings on the association between this chemical class and the SSR and possible opposing directions toward infant sex depending upon partners (i.e., paternal versus maternal exposure) or hormonal activities (i.e., estrogenic versus anti-estrogenic) of PCB congeners (Nieminen et al., 2013; Taylor et al., 2007; Terrell et al., 2011). With regard to OCPs, the effects of exposure to dibromochloropropane (DBCP) (Potashnik et al., 1984; Potashnik and Porath, 1995), dichlorodiphenyltrichloroethane (DDT) (Cocco et al., 2005, 2006; Salazar-García et al., 2004), and hexachlorobenzene (HCB) (Jarrell et al., 2002; Khanjani and Sim, 2006) on the SSR have been evaluated in several studies, with paternal exposure to DBCP being somewhat consistently associated with the reversal of the SSR (Potashnik et al., 1984; Potashnik and Porath, 1995). However, there have been few studies assessing both paternal and maternal preconception exposure to POPs in relation to the SSR as an approach to ensuring the temporal order of offspring sex determination. To investigate the potential effects of preconception exposure to POPs on human sex selection, we designed the Longitudinal Investigation of Fertility and the Environment (LIFE) Study of multiple classes of POPs and the SSR. By design, a total of 56 POPs measured prior to conception in both male and female partners were assessed in relation to the SSR in accordance with the couple-dependent nature of human conception.

2. Materials and methods

2.1. Study population

The LIFE Study is a prospective cohort study designed to investigate environmental influences on human fecundity and fertility, as previously described in detail (Buck Louis et al., 2011b). Briefly, 501 couples discontinuing contraception and trying for pregnancy were recruited from 16 counties in Michigan and Texas from 2005 to 2009, who were prospectively followed until pregnant or 12 months of attempting pregnancy. Women who became pregnant during the 12 months of follow-up were additionally followed to delivery or through a pregnancy loss. The eligibility criteria for participation were as follows: a) females aged 18–40 years and males aged 18 and older years; b) couples in a committed relationship; c) couples who were able to communicate in English or Spanish; d) females' menstrual cycles ranging from 21 to 42 days; e) no use of injectable contraceptives within 12 months; and f) no history of physician-diagnosed infertility or sterilization procedures. Of the couples enrolled in the LIFE Study, 235 (46.9%) couples who had a singleton birth were used for the present study, excluding 2 (0.4%) couples who had multiple births and 264 (52.7%) couples without an observed live birth during the follow-up period. Institutional review board approvals were obtained from all collaborating institutions. Written informed consent was provided by all study participants prior to study participation.

2.2. Data collection

Baseline data were collected by research assistants in the couples' home. Upon recruitment, the female partner provided a urine sample, which was used for a home pregnancy test to ensure that she was not pregnant. In-person interviews were conducted with each partner of the couple to ascertain socio-demographic characteristics (i.e., age, race/ethnicity, education, and annual household income) and reproductive history (i.e., parity and number of pregnancies fathered). Non-fasting blood (approximately 20 mL) was obtained from each partner of the couple for the quantification of serum concentrations of POPs and lipids. The blood samples were shipped on ice to the study's laboratory and kept frozen at −20 °C or colder until analysis. Couples who had a live birth during the follow-up period were asked to return standardized birth announcements following delivery to ascertain birth outcomes (i.e., infant sex, birth size, delivery mode, and date of birth).

2.3. Laboratory analysis

All analyses were conducted by the Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention. Specifically, couples' serum concentrations (ng/g) were measured using isotope dilution high-resolution mass spectrometry for the following chemicals: a) 9 OCPs (HCB; β-hexachlorocyclohexane [β-HCH]; γ-hexachlorocyclohexane [γ-HCH]; oxychlordane; *trans*-nonachlor; o,p′-DDT; p,p′-DDT; p,p′-dichlorodiphenyldichloroethylene [p,p′-DDE]; and mirex); b) 1 PBB (PBB 153); c) 10 PBDEs (congeners #17, 28, 47, 66, 85, 99, 100, 153, 154, and 183); and d) 36 PCBs (congeners #28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 114, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 201, 206, and 209). Standard operating procedures were used for the quantification of a total of 56 serum POP concentrations, inclusive of ongoing quality assurance and control procedures (Sjödin et al., 2004). The limits of detection (LODs) varied by analyte, ranging from 0.003 to 0.01 ng/g. All machine-observed values for serum chemical concentrations were utilized for analysis without automatic substitution of concentrations below the LODs or lipid adjustment to preclude bias associated with such practices (Richardson and Ciampi, 2003; Schisterman et al., 2006). Serum cotinine concentrations (ng/mL) were quantified using liquid chromatography-isotope dilution tandem mass spectrometry (Bernert et al., 1997) to assess baseline exposure to smoking. Serum lipids (ng/g) were quantified using commercially available enzymatic methods (Akins et al., 1989) and established calculation methods based on individual components including total cholesterol, free cholesterol, triglycerides, and phospholipids (Phillips et al., 1989).