Preconception Maternal and Paternal Exposure to Persistent Organic Pollutants and Birth Size: The LIFE Study

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BACKGROUND: Persistent organic pollutants (POPs) are developmental toxicants, but the impact of both maternal and paternal exposures on offspring birth size is largely unexplored.

OBJECTIVE: We examined associations between maternal and paternal serum concentrations of 63 POPs, comprising five major classes of pollutants, with birth size measures.

METHODS: Parental serum concentrations of 9 organochlorine pesticides, 1 polybrominated biphenyl (PBB), 7 perfluoralkyl chemicals (PFCs), 10 polybrominated diphenyl ethers (PBDEs), and 36 polychlorinated biphenyls (PCBs) were measured before conception for 234 couples. Differences in birth weight, length, head circumference, and ponderal index were estimated using multiple linear regression per 1-SD increase in natural log-transformed (ln-transformed) chemicals. Models were estimated separately for each parent and adjusted for maternal age, maternal prepregnancy body mass index (kilograms per meter squared) and other confounders, and all models included an interaction term between infant sex and each chemical.

RESULTS: Among girls (n = 117), birth weight was significantly lower (range, 84–195 g) in association with a 1-SD increase in ln-transformed maternal serum concentrations of DDT, PBDE congeners 28 and 183, and paternal serum concentrations of PBDE-183 and PCB-167. Among boys (n = 113), maternal (PCBs 138, 153, 167, 170, 195, and 209 and perfluorooctane sulfonamide) and paternal (PCBs 172 and 193) serum concentrations of several POPs were statistically associated with lower birth weight (range, 98–170 g), whereas paternal concentrations of PBDEs (66, 99) were associated with higher birth weight. Differences in offspring head circumference, length, and ponderal index were also associated with parental exposures.

CONCLUSIONS: Preconceptional maternal and paternal concentrations of several POPs were associated with statistically significant differences in birth size among offspring.

Introduction

The presence of persistent organic pollutants (POPs) in maternal blood (Llop et al. 2010; Rodriguez-Dozal et al. 2012; Rudge et al. 2012; Wang et al. 2009), umbilical cord blood (Arbuckle et al. 2013; Foster et al. 2011), and breast milk (Mikes et al. 2012; Pan et al. 2009; Tanabe and Kunisue 2007) documenting in utero and lactational exposure has prompted epidemiological studies to examine the relationship between exposure to these compounds and fetal growth and development (Mattison 2010; Windham and Fenster 2008). Research in this area has generally focused on outcomes such as birth weight and length of gestation, strong indicators of neonatal health. Epidemiological studies have shown a decrease in birth weight in relation to exposure to POPs that include polychlorinated biphenyls (PCBs) (Govarts et al. 2012; Karmaus and Zhu 2004; Murphy et al. 2010), polychlorinated diphenyl ethers (PBDEs) (Harley et al. 2011), perfluoralkyl chemicals (PFCs) (Washino et al. 2009), and organochlorine pesticides (OCPs) (Wolff et al. 2007). Although the previous studies have demonstrated an association between POPs and reduced birth size, proxied by birth weight, findings are inconsistent and studies have also reported null associations (Farhang et al. 2005; Givens et al. 2007; Karmaus and Zhu 2004; Kezios et al. 2012; Longnecker et al. 2005; Mazdai et al. 2003; Olsen et al. 2009; Pan et al. 2009; Sweeney and symanski 2007; Tan et al. 2009; Wu et al. 2010).

Inconsistencies may be attributed to several key limitations of prior studies. Past research has focused on pre- and postnatal exposures to POPs, despite evidence that the preconception period may be a critical window of exposure for fetal growth and development (Chapin et al. 2004). Given the metabolic and physiological changes that occur during pregnancy, preconception levels may be more accurate in capturing the dose to the fetus. Regardless of their long half-lives and persistent nature, the concentrations of pollutants may vary across critical windows of development, as seen with PCBs (Bloom et al. 2007) and other selected POPs (Wang et al. 2009). Finally, prior studies have focused on elucidating the impact of maternal exposure to POPs on birth size, regardless of the fact that pregnancy is a couple-dependent outcome. Consequently, the impacts of parentally mediated factors on birth size have been largely unstudied (Cordier 2008; Shah and Knowledge Synthesis Group on Determinants of Preterm/Low Birthweight Births 2010). Limited to occupational studies, little is known about the impact of paternal POP exposures on birth size (Lawson et al. 2004; Michalek et al. 1998).

We aim to address these gaps in knowledge by estimating the associations of maternal and paternal preconceptional serum concentrations of POPs on birth size. We hypothesize that preconceptional serum concentrations of both maternal and paternal persistent environmental chemicals are associated with reduced birth size measures (i.e., birth weight, head circumference, length, and ponderal index).

Methods

Study population. The Longitudinal Investigation of Fertility and the Environment (LIFE) Study was a prospective cohort study conducted between 2005 and 2009 to assess the impact of persistent environmental chemicals on reproductive outcomes (Buck Louis et al. 2011). Briefly, LIFE recruited couples (n = 501) who resided in Michigan and...
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Texas with reported or presumed exposure to persistent environmental chemicals. Married couples or those in a committed relationship who were planning a pregnancy in the subsequent 6 months were targeted for recruitment. Couples were ineligible to participate if either partner was medically/surgically sterile; they had discontinued contraception for > 2 months; the female’s menstrual cycle was not between 21 and 42 days or she had received injectable contraceptives within the previous 12 months; they were not of reproductive age (females < 18 or > 40 years, and males < 18 years); or they could not communicate in English or Spanish. Couples were followed until a positive human chorionic gonadotropin (hCG) pregnancy test or through 12 months of attempting pregnancy. Following conception, women were followed daily for 8 weeks and then monthly until a pregnancy loss or delivery. Analyses were restricted to couples for whom a singleton delivery was observed (n = 247), regardless of a previous loss, and for whose child birth weight was reported (n = 234). In doing so, we excluded data for two sets of twin births.

Institutional review board approval was obtained from all collaborating institutions, and informed written consent was obtained from all couples before their participation.

Assessment of fetal growth outcomes and covariates. Couples were asked to report birth size characteristics for the index birth using standardized birth announcements specifically designed for the LIFE study that were included in the pregnancy diary (available on request). Women were trained in their use and completed them after delivery. Information recorded on the delivery cards included infant sex, birth weight (in grams or pounds and ounces) (n = 230), length (in centimeters or inches) (n = 229), and head circumference (in centimeters or inches) (n = 181). Ponderal index (n = 229), a marker of asymmetrical growth retardation thought to be a result of fetal insult, was defined as 100 × [birth weight (grams)/length (cubic centimeters)] (Sparks et al. 1998). Analyses did not include infants whose birth weight (n = 2) or head circumference (n = 2) exceeded the 99th percentile.

Baseline questionnaires were administered to each partner separately and were used to collect medical and reproductive histories. Information on lifestyle factors such as the use of alcohol and tobacco in the previous 12 months was also collected. Participants then underwent an anthropometric assessment (Lohman et al. 1988) for measurement of their height and weight. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters squared).

Daily journals captured data on lifestyle factors, sexual intercourse, and home pregnancy test results. A fertility monitor captured data on peak luteinizing hormone concentrations indicative of ovulation. These data combined with information on sexual intercourse and positive hCG pregnancy test results allowed for the estimation of day of conception and, thereafter, gestational age. Pregnant women were asked to complete daily pregnancy journals that captured information on weight gain and gravid diseases (e.g., gestational diabetes).

Exposure assessment. Biospecimens were collected from each partner during the baseline home visit. Approximately 20 mL of nonfasting blood were collected to measure concentrations of environmental chemicals. For quality control, blood collection equipment was tested and determined to be free from contaminants under study. Quantification of serum toxicants was conducted by the Division of Laboratory Sciences in the National Center for Environmental Health at the Centers for Disease Control and Prevention (CDC). A list of all congeners measured and their abbreviations can be found in Table 1. Established protocols using isotope dilution gas chromatography–high resolution mass spectrometry (Barr et al. 2003; Kuksenky et al. 2005; Sandau et al. 2003) were used to estimate serum concentrations of 1 polybrominated biphenyl (PBB), 9 OCPs, 10 PBDEs, 36 PCBs, and 7 PFCs. Liquid chromatography–isotope dilution tandem mass spectrometry (Bernert et al. 1997) was used to quantify serum concentrations of cotinine (nanograms per milliliter), as a measure of tobacco exposure. Enzymatic methods were used to estimate total cholesterol, nonesterified cholesterol, triglycerides, and phospholipids (Akins et al. 1995). Total serum lipids (nanograms per gram serum) were calculated using established summation methods (Bernert et al. 2007; Phillips et al. 1989). Serum lipid concentrations were included in models as a covariate, and pollutant concentrations are reported in nanograms per gram serum, except for PFCs and cotinine, which are reported in nanograms per milliliter.

Statistical analyses. We assessed the distributions of all exposures and relevant covariates. Normality of continuous variables was assessed using Kolmogorov–Smirnov tests. Missing covariate values and missing chemical, cotinine, and lipid data (< 4%), due to insufficient blood for analysis, were imputed under the missing at random assumption, using Markov chain Monte Carlo methods (Rubin 1996) detailed elsewhere (Buck Louis et al. 2013). Machine-read values for chemical concentrations were used, and values below the limit of detection were not substituted to avoid introducing bias (Schisterman et al. 2006). To account for skewed distribution and for ease of interpretation, chemical concentrations were natural log-transformed (ln) and rescaled by their standard deviation. Geometric means (GMs) and 95% confidence intervals (CIs) were calculated for all chemicals. See Supplemental Material, Table S1, for a list of SDs and GMs for this study population. The outcome variables, birth weight (grams), head circumference (centimeters), length (centimeters), and ponderal index (grams per cubic centimeter) were not ln-transformed. Each outcome and chemical concentration was modeled as a continuous variable.

We used multiple linear regression to estimate the mean difference in each outcome per 1-SD increase for all ln-transformed chemicals. The mean differences in growth outcomes for each chemical and parent were estimated separately. Models were adjusted a priori for maternal age, the difference between maternal and paternal age, maternal prepregnancy BMI, infant sex, serum lipids (except PFCs), and serum cotinine concentrations (Cliver et al. 1995; Cogswell and Yip 1995; Shah and Knowledge Synthesis Group on Determinants of Preterm/Low Birthweight Births 2010). The sum of the remaining chemical concentrations (ln-transformed and scaled by their respective standard deviation) in each chemical’s respective class was included in models to account for the mean level of individual concentrations.

Table 1. Persistent organic pollutants (POPs) measured in study population, LIFE Study, 2005–2008.

| POPs | Compounds or congeners |
|------|------------------------|
| Polybrominated biphenyls (PBBs) | PBB-153, Hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCH), γ-hexachlorocyclohexane (γ-HCH), oxychlordane, trans-nonachlor, mirex, p,p'-DDT, p,p'-DDE, and p,p'-DDE |
| Organochlorine pesticides (OCPs) | PCBs 12, 18, 28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 114, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 196, 198, 201, 206, 209 |
| Polychlorinated diphenyl ethers (PBDEs) | PBDEs 12, 17, 19, 21, 28, 33, 37, 47, 66, 85, 99, 100, 153, 154, 183 (non-dieldrin) |
| Polychlorinated biphenyls (PCBs) | PCBs 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, 196, 198, 201, 206, 209 |
| Perfluoroalkyl chemicals (PFCs) | 2-(ethyl-perfluorooctanoate sulfonamide) acetate (Et-PFOA-AcOH), 2-(N-methyl-perfluorooctanoate sulfonamide) acetate (Me-PFOA-AcOH), perfluorodecanoate (PFDeA), perfluorooctanoate (PFNA), perfluorooctane sulfonamide (PFOS), perfluorooctane sulfonate (PFOS), and perfluorooctanoate (PFOA) |
for the partner’s exposure, each model also included the total sum of partner’s serum concentrations in the respective class for the chemical being evaluated. Interaction between each pollutant and infant sex was evaluated by examining the statistical significance of their product term in each model (p < 0.05). Evidence of interaction between chemical exposures and birth outcomes by infant sex was observed for some chemicals and models by significant interaction term (p-interaction < 0.05), so all associations were estimated stratified by sex for consistency. We report associations for chemicals for which at least one statistically significant association was estimated with birth size measures. Statistical significance was set at p < 0.05.

We conducted a sensitivity analysis that excluded pregnancies complicated by gestational diabetes or hypertension because of their known effects on fetal growth (Mayer and Joseph 2013). Results and conclusions of the association between parental preconception exposure to persistent organic pollutants and birth size measures did not vary (data not shown). Therefore, model estimates that include all pregnancies are reported.

Results

Study population. Partners for whom a singleton delivery occurred were very similar in their sociodemographic characteristics (Table 2). The majority of men and women were non-Hispanic white, had a college education, were insured, and did not smoke or drink alcohol. Compared with their female counterparts, males were approximately 2 years older and on average had a higher BMI (29.3 vs. 26.5 kg/m²). Women reported having gestational diabetes mellitus (n = 27), hypercholesterolemia (n = 18), and preexisting hypertension (n = 7). The majority of infants were girls (51%). The mean (± SD) postconception gestational age and birth weight of infants at delivery was 36.2 ± 2.2 weeks and 3382.3 ± 487.5 g, respectively.

Serum concentrations of most POPs among couples were similar for partners. However, geometric mean concentrations of pesticides such as p,p′-DDE (dichlorodiphenylchloroethylene) (0.580 ng/g; 95% CI: 0.534, 0.630 vs. 0.752 ng/g; 95% CI: 0.700, 0.808), mirex (0.007 ng/g; 95% CI: 0.007, 0.008 vs. 0.013 ng/g; 95% CI: 0.011, 0.014), and several PFCs were markedly higher among males (see Supplemental Material, Table S1). Preconceptional parental concentrations of POPs were found to be associated with changes in birth size measures.

OCPs and PBDEs. Statistically significant differences in birth size measures were estimated in association with both maternal and paternal preconception serum concentrations of OCPs among girls, but virtually no significant associations were observed among boys (Table 3). See Supplemental Material, Tables S2–S5, for all estimated associations for birth size measures and chemicals evaluated in our study. Among girls, a 1-SD increase in ln-transformed maternal serum concentrations of p,p′-DDT (dichlorodiphenyltrichloroethane) was associated with lower birth weight (β = 195.39 g; 95% CI: –351.25, –39.52), driven perhaps by smaller head circumference (β = –0.78 cm; 95% CI: –1.48, –0.09). Smaller head circumference was also seen with increasing paternal concentrations of β-HCH (hexachlorocyclohexane) (β = 1.47 cm; 95% CI: –2.33, –0.61). Length among girls was inversely associated with maternal concentrations of γ-HCH (lindane) and subsequently higher ponderal index (β = 0.09 g/cm²; 95% CI: 0.03, 0.16). Similarly, paternal concentrations of γ-HCH were associated with shorter length and higher ponderal index among girls, despite mutual adjustment for mean partner concentrations of other organochlorine exposure. A higher ponderal index among girls was also seen with increasing paternal concentrations of p,p′-DDE. Except for larger head circumference observed with increasing maternal concentrations of HCB (hexachlorobenzene), preconceptional parental concentrations of OCPs were not associated with birth size among boys. Parental preconception concentrations of PBB-153 were not found to be associated with birth size measures.

PCBs. The mean birth weight of boys was 104.23 g lower (95% CI: –194.16, –14.30) for every 1-SD increase in ln-transformed maternal concentrations of PFOA (perfluorooctanoic acid). Maternal concentrations of the Et-PFOA-AcOH [2-(n-ethyl-perfluorooctanoic acid) acetate] metabolite were associated with a smaller mean ponderal index among girls (–0.09 g/cm²; 95% CI: –0.16, –0.02). We did not observe associations between preconceptional paternal concentrations of PFCs and birth measures. Furthermore, preconceptional parental concentrations of PFCs were not associated with length or head circumference at birth.

PBDEs. Maternal concentrations of PBDEs were associated with significant differences in mean birth weight in boys and girls. Maternal concentrations of PBDE congener 28 and 183 were associated with lower birth weight among girls; the largest negative association was estimated for PBDE-28 (β = –151.33 g; 95% CI: –298.56, –4.10). Maternal concentrations of PBDE-28 were also statistically associated with smaller length and head circumference among girls. On the contrary, for every 1-SD increase in ln-transformed maternal concentrations of PBDEs 66 and 99, mean birth weight among boys was 125.04 g (95% CI: 18.16, 231.92) and 133.39 g (95% CI: 9.12, 257.37) higher, respectively. Among boys, PBDE congeners were also statistically associated with larger length (PBDE-99) and head circumference (PBDEs 66, 85, 99). As seen with maternal concentrations, paternal concentrations of PBDE-183 were also significantly associated with lower birth weight among girls (β = –92.13 g; 95% CI: –173.44, –10.82).

PCBs. Among girls, maternal concentrations of PCBs were not associated with significant differences in birth weight. However, for every 1-SD increase in ln-transformed concentrations of paternal concentrations of PCB-167, the mean birth weight among girls was 97.49 g lower (95% CI: –187.45, –7.54), and mean length (β = –0.57 cm; 95% CI: –1.12, –0.02) and head circumference (β = –0.45 cm; 95% CI: –0.86, –0.03) were smaller. Significant associations between parental concentrations of PCBs and birth size were more frequent among boys. Birth weight among boys was lower by 99–170 g for 1-SD increase in ln-transformed maternal concentrations of PCBs 138, 153, 167, 170, 195, and 209) and paternal (PCBs 172, 195) concentrations. Maternal concentrations of PCBs were statistically associated with smaller head

Table 2. Description of study cohort by partner among those with a singleton delivery (n = 234), LIFE Study, 2005–2009 [n (%) or mean ± SD].

| Characteristic | Mother | Father |
|---------------|--------|--------|
| Race/ethnicity | Non-Hispanic white | 194 (84) | 198 (85) |
| | Non-Hispanic black | 2 (1) | 4 (2) |
| | Hispanic | 20 (9) | 20 (9) |
| | Other | 16 (7) | 12 (5) |
| Education | High school | 0 (0) | 2 (1) |
| | High school/equivalent | 9 (4) | 5 (2) |
| | College | 223 (98) | 225 (97) |
| Health insurance | No | 5 (2) | 10 (4) |
| | Yes | 227 (98) | 223 (96) |
| Smoking status at baseline* | Active (cotinine ≥ 100 ng/mL) | 11 (5) | 24 (10) |
| | Passive (cotinine < 100 ng/mL) | 219 (95) | 205 (90) |
| Cigarettes smoked (9–12 weeks) | None | 227 (98.8) | — |
| | < 10 | 2 (0.8) | — |
| | ≥ 10 | 1 (0.4) | — |
| Alcohol use at baseline** | No | 52 (22) | 31 (13) |
| | Yes | 182 (78) | 203 (87) |
| Alcohol use (9–12 weeks) | None | 229 (99.6) | — |
| | 1 drink/week | 1 (0.4) | — |
| | Age (years)* | 29.8 ± 3.7 | 31.5 ± 4.6 |
| | Body mass index (kg/m²)* | 26.4 ± 6.5 | 29.3 ± 5.3 |
| | Parity | 1.1 ± 1.2 | 1.0 ± 1.1 |

All characteristics are self-reported except for body mass index. Missing covariate data was not included in table.

*p = 0.005.
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Paternal concentrations of PCBs were also significantly associated with smaller head circumference among girls (PCBs 128, 138, 153). Paternal concentrations of PCBs 128, 138, 153 were estimated to be associated with significantly smaller mean head circumference and ponderal index among boys and girls. Paternal concentrations of PCB-138 were associated with lower mean birth weight among boys and smaller mean head circumference and ponderal index among boys and girls. Paternal concentrations of PCB-138 were estimated to be associated with smaller mean ponderal index among boys. Additionally, in girls, paternal concentrations of PCB-156 and in boys maternal (PCBs 170, 172) and paternal (PCBs 156, 157) PCB concentrations were associated with smaller ponderal index (range, 0.08–0.13 g/cm³).

Persistent organic pollutants associated with multiple birth size outcomes. Both maternal and paternal concentrations of several persistent organic pollutants were associated with statistical differences in the same birth size measure among their offspring. The statistical differences associated with increasing parental concentrations of these pollutants were often of similar magnitude and direction. We briefly highlight these compounds here.

Lower mean birth weight was observed in association with increasing preconception paternal and maternal concentrations of PBDE-183 among girls and PCBs 128 and 195 among boys. Maternal concentrations of PCB-167 were associated with lower mean birth weight among girls only, but paternal concentrations were associated with lower birth weight in boys. Increasing maternal and paternal concentrations of 1,2,3-Trichlorobenzene were associated with smaller head circumference and higher ponderal index among girls.

Discussion

In this prospective pregnancy study with preconception enrollment of couples, we demonstrated that both preconception maternal and paternal serum concentrations of persistent organic pollutants were

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Table 3. Adjusted² mean changes (β) and their 95% CIs for each birth size measure per 1-SD increase in ln-transformed chemical concentration² by partner and infant sex, LiFE Study, 2005–2009.

| Outcome                                   | Maternal                          | Paternal                          |
|-------------------------------------------|-----------------------------------|-----------------------------------|
| Birth weight (g)                          |                                   |                                   |
| µ-DDE                                    | -0.19 (95% CI)                    | -0.08 (95% CI)                    |
| PCB-28                                   | -0.13 (95% CI)                    | -0.11 (95% CI)                    |
| PCB-66                                   | -0.17 (95% CI)                    | -0.13 (95% CI)                    |
| PCB-96                                   | -0.10 (95% CI)                    | -0.10 (95% CI)                    |
| PCB-183                                  | -0.14 (95% CI)                    | -0.14 (95% CI)                    |
| PCB-138                                  | -0.12 (95% CI)                    | -0.16 (95% CI)                    |
| PCB-153                                  | -0.11 (95% CI)                    | -0.13 (95% CI)                    |
| PCB-167                                  | -0.10 (95% CI)                    | -0.10 (95% CI)                    |
| PCB-170                                  | -0.10 (95% CI)                    | -0.09 (95% CI)                    |
| PCB-172                                  | -0.10 (95% CI)                    | -0.08 (95% CI)                    |
| PCB-195                                  | -0.10 (95% CI)                    | -0.08 (95% CI)                    |
| PCB-201                                  | -0.10 (95% CI)                    | -0.07 (95% CI)                    |
| PCB-206                                  | -0.09 (95% CI)                    | -0.05 (95% CI)                    |

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²Results are presented only for chemicals for which at least one statistically significant association between pollutants and birth size measures were estimated. Models are adjusted for maternal and paternal serum lipids, serum cotinine, maternal prepregnancy BMI (kg/m²), maternal age, difference in parental age, infant sex, and the individual and partner sum of remaining chemical concentrations in each chemical’s respective class. * Restricted to chemicals with a significant association with fetal growth outcomes. ¶ For data on 113 boys and 117 girls were available for analysis. ¶ For data on 113 boys and 119 girls were available for analysis. * p < 0.05 for parent concentration and infant sex interaction term.
significantly associated with birth size measures among their offspring, even after taking into account their partner’s serum concentrations. In addition, we also report several statistically significant differences in birth size measures by infant sex and between and within classes of pollutants. We observed decreases in infant birth weight between 85 and 195 g with 1-SD increases in preconception maternal and paternal serum concentrations of POPs.

This reduction is similar in magnitude to what has been reported for other prenatal maternal environmental exposures. Compared with nonsmokers, lower mean birth weight has been reported for infants born to women who reported cigarette smoking during the first trimester or throughout pregnancy (range, 55–189 g) (Cliver et al. 1995). Meta-analyses have reported lower birth weight among infants born to nonsmoking women exposed to environmental tobacco smoke (33 g; 95% CI: 16, 51) (Leonardi-Bee et al. 2011) and in association with increasing cord serum concentrations of PCB-153 (150 g; 95% CI: 50, 250) (Govarts et al. 2012). Last, a meta-analysis reported that when compared with lower exposure groups, women exposed to higher mean levels of indoor air pollution from solid fuel use had infants whose birth weight was approximately 96.6 g lower (95% CI: 68.5, 124.7) (Pope et al. 2010).

Our findings underscore the importance of designing epidemiological studies that ascertain preconception parental exposures in relation to birth size measures. In addition, given that paternal environmental exposures are often overlooked when examining the associations between parental exposures and fetal growth, there is a need for more comprehensive investigations of the associations between preconception paternal exposures and fetal growth and development. Both maternal and paternal serum concentrations of several pollutants (PBDE-183, PCBs 128, 138, 167, and 195, and γ-HCH) were associated with birth size measures, but more research is needed to investigate whether associations that were specific to paternal serum concentrations are relevant and can be confirmed in other populations.

Few prospective pregnancy studies report parental preconception serum concentrations of POPs, making it difficult to further evaluate our findings. The only known study to examine the association between preconception maternal PCB levels and birth weight was conducted using data obtained from a prospective cohort of New York women and their partners planning a pregnancy within the next 6 months (Murphy et al. 2010). After adjustment for maternal height, smoking, and infant sex, the birth weight of infants (n = 50) born to mothers with the highest concentrations of antiestrogenic PCBs [interquartile range (IQR): 0.23–0.33 ng/g serum] was approximately 471 g (95% CI: –890.2, –51.3) lighter than infants born to mothers with the lowest concentrations (IQR: 0.13–0.15 ng/g serum). This study also examined the association between infant birth weight and maternal antiestrogenic PCB concentrations from serum measured during the prenatal period (median, 6 weeks gestation). The mean difference in infant birth weight between women with the highest (IQR: 0.15–0.21 ng/g serum) and lowest (IQR: 0.07–0.09 ng/g serum) prenatal concentrations of maternal antiestrogenic PCBs was approximately 260 g less (β = –260.5; 95% CI: –667.4, 146.5) than what was reported for preconception levels (Murphy et al. 2010).

Given the debate about classifying chemicals by their action, which may also be a function of dose, we decided to examine each individually. By doing so, we did not make any assumptions regarding their hypothesized biologic activity or how compounds may interact with each other in mixture form. However, in our present study we report statistically significant associations between birth size measures and two PCB congeners. For one previously shown to be estrogenic (PCB-153), we found that maternal concentrations were significantly associated with lower birth weight and head circumference in boys; for another, shown to be antiestrogenic (PCB-156), we found paternal concentrations to be associated with lower ponderal index in both boys and girls (Cooke et al. 2001). We also observed associations between birth weight and lower serum concentrations of PCBs than what has been previously published in a study of New York anglers and their partners planning a pregnancy, mentioned above (Murphy et al. 2010). It has been shown that serum concentrations of POPs in the LIFE study population (Buck Louis et al. 2013) are lower than reported for the U.S. population (CDC 2014). This difference is not surprising given that concentrations of persistent chemicals increase with age and the LIFE cohort is comprised of couples of reproductive age, unlike the NHANES population that comprises women 12–85 years of age.

Our study also reports several positive associations between pollutants and birth size measures. Maternal concentrations of PBDEs 66 and 99 were associated with increased mean birth weight, length, and head circumference among boys only. Maternal concentrations of PCBs 201 and 206 and maternal and paternal concentrations of OCPs were associated with increased mean head circumference and ponderal index among girls only. Although they are not comparable to our study, other studies have reported positive associations between maternal prenatal levels of environmental chemicals. Maternal prenatal concentrations of total PCBs and PBBS (congener specific information not available) have been associated with higher birth weight (Sweeney and Symanski 2007). Positive associations between head circumference and length have also been reported for maternal prenatal levels of organophosphate pesticides not evaluated in this study (Ekenazi et al. 2004). Associations reported by these studies also differed by sex. We are unable to explain these findings, but posit that they may reflect differing structural activity or biological activity of individual congeners, particularly given that associations differed by infant sex. Also, the windows of vulnerability for a fetus’s growth and development may differ by congener. We also speculate that these positive associations may be confounded by healthy behaviors such as the consumption of fish or antioxidant-rich foods. These healthy behaviors, although potential sources of parental POP exposure, may also positively influence fetal growth and development.

Our study addressed several key limitations of prior studies with equivocal findings of the association between prenatal exposure to POPs and birth size. For one, many studies ascertained prenatal exposure to POPs during late pregnancy using maternal serum concentrations at the time of delivery or using umbilical cord serum concentrations. These studies may not be capturing exposure during relevant windows of fetal growth and development. Prospective pregnancy cohort studies that recruit couples discontinuing contraception to become pregnant are rare, and this is the only way to examine the association between preconception exposures to POPs and human birth size. Despite their long half-lives, maternal serum concentrations of PCBs and selected POPs can vary across critical windows of human reproduction and development during pregnancy (Bloom et al. 2007; Wang et al. 2009). Preconception maternal serum concentrations are not influenced by the expansion of blood volume and changes in metabolism associated with normal pregnancy. Thus, we can explore associations with birth size measures in relation to exposure that reflects preconception and early pregnancy, a key window for these effects.

Prior studies have focused on maternal exposures and how they impact developmental health. Maternal exposures to POPs have been largely unstudied, and little is known about their potential impact on fetal development and growth. Environmental chemical exposures that occur during spermatogenesis may affect the quality of a father’s gametes, and therefore may affect the susceptibility and health of his offspring in utero or after birth (Olshan and Faustman...
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REFERENCES

Adegoye AR, Heitmann B. 2008. Accuracy and correlate of maternal recall of birthweight and gestational age. BJOG 115:886–893.

Akins JR, Waldrep K, Bernert JT Jr. 1989. The estimation of total serum lipids by a completely enzymatic ‘summation’ method. Clin Chim Acta 184:219–226.

Anderson D. 2005. Male-mediated developmental toxicity. Toxicol Appl Pharmacol 207(2 suppl):S506–S513.

Aruckle TE, Kubwabo C, Walker M, Davis K, Lalonde K, Krosarc I, et al. 2013. Umbilical cord blood levels of perfluorinated acids and polybrominated flame retardants. Int J Hyg Environ Health 218:184–194.

Barr JR, Magglo VL, Barr DB, Turner WE, Sijodia A, Sandau CD, et al. 2003. New high-resolution mass spectrometric approach for the measurement of polychlorinated biphenyls and organochlorine pesticides in human serum. J Chromatogr B Analyt Technol Biomed Life Sci 794:137–148.

Bat-Erdene U, McFarlane A, McDonald SW, Trough SC. 2013. Validation of Canadian mothers’ recall of events in labour and delivery with electronic health records. BMC Pregnancy Childbirth 13(suppl 1):S3; doi:10.1186/1471-295X-13-S1-S3.

Bernett JT, Turner WE, Patterson DG Jr, Needham LL. 2007. Calculation of serum “total lipid” concentrations for the adjustment of persistent organo halogen toximetric measurements in human samples. Chemosphere 68:234–251.

Bernett JT Jr, Turner WE, Pirkle JL, et al. 1997. Development and validation of sensitive method for determination of serum cotinine in smokers and nonsmokers by liquid chromatography/atmospheric pressure ionization tandem mass spectrometry. Clin Chem 43:2281–2291.

Bloom MS, Buck Louis GM, Schisterman EF, Liu A, Kostyniak PJ. 2007. Maternal serum polychlorinated biphenyl concentrations across critical windows of human development. Environ Health Perspect 115:1320–1324; doi:10.1289/ehp.100866.

Buck Louis GM, Schisterman EF, Sweeney AM, Wilcosky TC, Gore-Langton RE, Lynch CF, et al. 2011. Designing prospective cohort studies for assessing reproductive and developmental outcomes during sensitive windows of human reproduction and development—the LIFE Study. Paediatr Perinat Epidemiol 25:413–424.

Buck Louis GM, Sundaram R, Schisterman EF, Sweeney AM, Lynch CF, Gore-Langton RE, et al. 2013. Persistent environmental pollutants and couple fecundity: the LIFE Study. Environ Health Perspect 121:231–236; doi:10.1289/ehp.1205301.

Buka SL, Goldstein JM, Spartos E, Tsuang MT, 2004. The retrospective measurement of prenatal and peri-natal events: accuracy of maternal recall. Schizophr Res 71:417–426.

CDC (Centers for Disease Control and Prevention). 2014. Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, Tables, September 2013. Atlanta, GA:National Center for Environmental Health; Division of Laboratory Sciences. Available: http://www.cdc.gov/exposurereport.[accessed 12 December 2014].

Chapin RE, Robbins WA, Schieve LA, Sweeney AM, Kuklenyik Z, Needham LL, Calafat AM. 2005. Calculation of serum “total lipid” concentrations for the adjustment of persistent organohalogen toximetric measurements in human samples. Chemosphere 68:234–251.

Cline SP, Goldstein RL, Ciborski GR, Hoffman HJ, Davis RD, Nelson KG. 1995. The effect of cigarette smoking on neonatal anthropometric measurements. Obstet Gynecol 85:625–630.

Cogswell ME, Yip R. 1995. The influence of fetal and maternal factors on the distribution of birthweight. Semin Perinatol 19:222–227.

Cook PE, Sato T, Buchanan DL. 2001. Disruption of steroid hormone signaling by PCBs. In: PCBs: Recent Advances in Environmental Toxicology and Health Effects (Robertson LW, Hansen LG, eds). Lexington, KY:University of Kentucky, 257–263.

Corder S. 2008. Evidence for a role of paternal exposure in developmental toxicity. Basic Clin Pharmacol Toxicol 102:176–181.

Curley JP, Mashhood R, Champagne FA. 2011. Epigenetics and the origins of paternal effects. Horm Behav 59:306–314.

Eskenazi B, Harley K, Bradman A, Weltzien E, Jewell NP, Barr DB, et al. 2004. Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. Environ Health Perspect 112:1116–1124; doi:10.1289/ehp.6789.

Farhang L, Weintraub JM, Petreas M, Eskenazi B, Bhatia R. 2005. Association of DDT and DDE with birth weight and length of gestation in the Child Health and Development Studies, 1959–1967. Am J Epidemiol 162:717–725.

Foster WG, Gregorovich S, Morrison KM, Atkinson SA, Kubwabo C, Stewart B, et al. 2011. Human maternal and umbilical cord blood concentrations of polychlorinated diphenyl ethers. Chemosphere 84:1301–1305.

Fullston T, Olhsson Teague EM, Palmer NO, DeBlasio MJ, Mitchell M, Corbett M, et al. 2013. Paternal obesity initiates metabolic disturbances in two generations of mice with incomplete pene- trance to the F2 generation and alters the transcription prole of testis and sperm microRNA content. FASEB J 27:4226–4233.

Givens ML, Small CM, Terrell ML, Cameron LL, Michels Blanck H, Tolbert PE, et al. 2007. Maternal exposure to polychlorinated and polbiphenyls: infant birth weight and gestational age. Chemosphere 69:1295–1303.

Govarts E, Nieuwenhuijsen MJ, Schoeters G, Ballester F, Blöomen K, de Boer M, et al. 2012. Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European birth cohorts. Environ Health Perspect 120:162–170; doi:10.1289/ehp.1103276.

Huy KG, Chevrier J, Aguilar Schall R, Sijdjin A, Bradman A, Eskenazi B. 2011. Association of prenatal exposure to polychlorinated diphenyl ethers and infant birth weight. Am J Epidemiol 174:885–892.

Karmaus W, Zhu X. 2004. Maternal concentration of polychlorinated biphenyls and dichlorodiphenyl dichloroethene and birth weight in Michigan fish eaters: a cohort study. Environ Health 3:1; doi:10.1186/1476-069X-3-1.

Kezios KL, Liu X, Cirillo PM, Kalantzi OL, Wang Y, Petreas MX, et al. 2012. Prenatal polychlorinated biphenyl exposure is associated with decreased gestational length but not birth weight: archived samples from the Child Health and Development Studies pregnancy cohort. Environ Health 11:49; doi:10.1186/1476-068X-11-49.

Kuklenyik Z, Needham LL, Calafat AM. 2005. Measurement of 18 perfluorinated organic acids and amides in human serum using on-line solid-phase extraction. Anal Chem 77:6085–6091.

Lawrence CC, Schnorr TM, Whelan EA, Deddens J, Dankovic DA, Piacielti LA, et al. 2004. Prenatal occupational exposure to 2,3,7,8-tetrachlorodibenzo- p-dioxin and birth outcomes of offspring: birth weight, preterm delivery, and birth defects. Environ Health Perspect 112:1403–1408; doi:10.1289/ehp.7051.
Leonardi-Bee J, Britton J, Venn A. 2011. Secondhand smoke and adverse fetal outcomes in nonsmoking pregnant women: a meta-analysis. Pediatrics 127:734–741.
Llop S, Ballestre F, Vizcaíno E, Murcia M, López-Espinosa MJ, Rebagliato M, et al. 2010. Concentrations and determinants of organochlorine levels among pregnant women in Eastern Spain. Sci Total Environ 408:5750–5767.
Lohman TG, Roche AF, Martorell R, eds. 1988. Anthropometric Standardization Reference Manual. Champaign, IL:Human Kinetics Books.
Longnecker MP, Klebanoff MA, Brock JW, Guo X. 2005. Maternal levels of polychlorinated biphenyls in relation to preterm and small-for-gestational-age birth. Epidemiology 16:641–647.
Mattison DR. 2010. Environmental exposures and development. Curr Opin Pediatr 22:208–218.
Mayer C, Joseph KS. 2013. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. Ultrasound Obstet Gynecol 41:136–145.
Mazdai A, Dodder NG, Abernathy MP, Hites RA, Mayer C, Joseph KS. 2013. Fetal growth: a review of determinants of organochlorine levels among pregnant women in Eastern Spain. Sci Total Environ 408:5750–5767.
Phillips DL, Pirkle JL, Burse VW, Bernert JT Jr, Henderson LD, Needham LL. 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol 18:495–500.
Pope DP, Mishra V, Thompson L, Siddiqui AR, Rehfuess EA, Weber M, et al. 2010. Risk of low birth weight and stillbirth associated with indoor air pollution from solid fuel use in developing countries. Epidemiol Rev 32:70–81.
Rodríguez-Dozal S, Riojas Rodríguez H, Hernández-Avila M, Van Oostdam J, Weber JP, Needham LL, et al. 2012. Persistent organic pollutant concentrations in first birth mothers across Mexico. J Expo Sci Environ Epidemiol 22:50–69.
Rubin DB. 1996. Multiple imputation after 18+ years. J Amer Statist Assoc 91:473–489.
Rudge CV, Sandanger T, Röllin HB, Calderon IM, Volpato G, Silva JL, et al. 2012. Persistent organic pollutant concentrations in first birth mothers across Mexico. J Expo Sci Environ Epidemiol 22:50–69.
Sandsau CD, Sjödin A, Davis MD, Barr JR, Maggio VL, Rubin DB. 1996. Multiple imputation after 18+ years. J Amer Statist Assoc 91:473–489.
Schisterman EF, Vexler A, Whitcomb BW, Liu A. 2006. The limitations due to exposure detection limits for regression models. Am J Epidemiol 163:374–383.
Shah PS, Knowledge Synthesis Group on Determinants of Preterm/Low Birthweight Births. 2010. Paternal factors and low birthweight, preterm, and small for gestational age births: a systematic review. Am J Obstet Gynecol 202:163–123.