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Paternal Exposures to Environmental Chemicals and Time-to-Pregnancy: Overview of Results from the LIFE Study

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Abstract

Published findings from the Longitudinal Investigation of Fertility and the Environment (LIFE) Study regarding the relation between environmental chemicals and couple fecundity, as measured by time-to-pregnancy (TTP), are reviewed with a particular focus on role of the male partner. The LIFE Study recruited 501 couples from 16 counties in two U.S. states upon discontinuing contraception for purposes of becoming pregnant. Upon enrollment, couples provided a blood and urine sample for the quantification of persistent and non-persistent environmental chemicals, respectively, and then completed daily journals until pregnant or up to one year of trying. Female partners used fertility monitors to aid the timing of intercourse relative to ovulation, and digital home pregnancy test kits on the day of expected menses. Chemical classes included: metals, persistent organic pollutants, environmental phenols, and phthalates that were quantified using...
inductively coupled plasma mass spectrometry or isotope dilution high resolution or tandem mass spectrometry. Time-to-pregnancy (TTP) was defined as the number of prospectively observed menstrual cycles required for pregnancy. Fecundability odds ratios (FORs) and 95% confidence intervals (CIs) were estimated for each chemical and partner after adjusting for potential confounders and accounting for right censoring and time off contraception. FORs <1 are suggestive of diminished fecundity or a longer TTP.

Significant reductions (ranging from 17% to 31%) in couple fecundity were observed for male partners’ concentration of lead (0.83; 0.70, 0.98), 2,2′,4,4′-tetrahydroxybenzophenone (0.69; 0.49, 0.97), monobenzyl (0.80; 0.67, 0.97) and monomethyl (0.81; 0.70, 0.94) phthalates after adjusting for the female partners’ concentrations. Seven PCB congeners quantified in men’s serum were associated with a 17% to 29% reduction in couple fecundity.

Our findings underscore the importance of a couple based exposure design, inclusive of the male partner, when assessing couple dependent outcomes such as TTP to avoid misinterpretation of results based only upon the female partner.

Introduction

Evolving data suggest that human fecundity may be declining (Skakkebaek et al. 2001, 2006) reflected in part by declining conception rates in some (Jensen et al. 2008) but not all geographic locations (Joffe et al. 2000; Scheike et al. 2008). Other findings suggestive of diminishing fecundity include regional differences in time-to-pregnancy (Jensen et al. 2001; Sanin et al. 2009) and semen quality (Swan et al. 2003; Rolland et al. 2013), increasing rates of male genital-urinary malformations (Chilvers et al. 1984; Paulozzi et al. 1997), increasing prevalence of gynecologic disorders such as endometriosis and polycystic ovarian syndrome (Bergman et al. 2012), and increasing rates of specific reproductive site cancers, such as testicular (Purdue et al. 2005; Znaor et al. 2015) and breast (Holford et al. 2006; Hery et al. 2008) cancers. Moreover, there is growing recognition that urologic and gynecologic disorders may be etiologically associated with a spectrum of later onset adult diseases, including cardiovascular disease and cancer. For example, cryptorchidism and infertility are associated with later onset testicular cancer (Baker et al. 2005; McGlynn and Trabert 2012; Trabert et al. 2013), while polycystic ovarian syndrome is associated with metabolic syndrome (Dahlgren et al. 1992; Shaw et al. 2008) and endometriosis with ovarian cancer (Kok et al. 2015). Despite these suggestive findings, lingering data gaps remain largely given the absence of reproductive surveillance systems for addressing global temporal patterns (Le Moal et al. 2015).

While authors have called for the collection of data to monitor human fecundity (Joffe 2003; Olsen and Rachootin 2003; te Velde et al. 2010) to answer lingering questions about secular patterns in men and women’s biologic capacity for reproduction, this is a challenging task in light of the important role of pregnancy related intentions and other behaviors in measuring time-to-pregnancy (TTP) at the population level. Accompanying the scientific inquiry about fecundity patterns as measured by TTP is a growing body of evidence suggesting that endocrine disrupting chemicals (EDCs) may adversely impact male and female fecundity, as measured by alterations in semen quality or menstrual cycles, longer TTPs, genital-urinary...
birth defects, pregnancy loss, and gynecologic disorders, as summarized elsewhere (Foster et al. 2008; Rocheleau et al. 2009; Bergman et al. 2012).

The purpose of this paper is to provide an overview of the findings from the LIFE Study regarding the relation between EDCs and couple fecundity, with a particular focus on male partners’ chemical concentrations, and to weigh the findings in the context of the current human fecundity literature.

**Material & Methods**

**Sampling framework and design**

The Longitudinal Investigation of Fertility and the Environment (LIFE) Study was designed specifically to assess the relation between EDCs and human fecundity and fertility in the context of lifestyle. The unique aspects of the LIFE Study was that it utilized a couple based sampling framework along with a prospective cohort design that recruited couples upon discontinuing contraception for purposes of becoming pregnant (Buck Louis et al. 2011). The LIFE Study built upon earlier couple based cohorts with preconception enrollment that demonstrated men could be successfully recruited and enrolled in fecundity oriented research (Bonde et al. 1998; Zinamen et al. 1996). Full human subjects approval was obtained from all participating institutions for the conduct of the LIFE Study, and informed consent was given by all study participants.

Couples were recruited from 16 counties in two U.S. states - Michigan and Texas. Letters of invitation were sent to couples who were then screened for eligibility: 1) in a committed relationship and planning a pregnancy in next 6 months; 2) female partner aged 18-40 years and male partner aged ≥18 years; 3) females had menstrual cycles between 21-42 days, no history of injectable hormonal contraception in past year, and not currently breastfeeding ≥6 months; 4) couple were discontinuing contraception or off <2 months; and 5) an ability to communicate in English or Spanish. Couples were excluded if either/both partners reported clinically diagnosed infertility and having been told it would be impossible to conceive without medical care.

**Data and biospecimen collection**

A home-based approach was used for all data collection. The research team comprised two trained assistants who conducted in-person interviews simultaneously with each partner of the couple followed by the measurement of height and weight using a standardized anthropometric protocol. Blood and urine samples were obtained from all participating couples, and all biospecimens were kept on ice through delivery to the research site's coordinating center for processing. Male partners were instructed in the collection of two semen samples approximately one month apart. Female partners were taught how to use the Clearblue® Fertility Monitor (Inverness Medical Innovations, Waltham, MA), which gives a visual prompt of “peak” fertility to help time intercourse relative to ovulation. The monitor is reported to be accurate in the detection of the LH surge relative to ultrasonology (Behre et al. 2000). Women were also taught to use the Clearblue® digital pregnancy test on the day of expected menses consistent with the manufacturer’s guidance. The digital kit is sensitive for
reliably detecting 25 mIU/mL of hCG with accurate home use by women (Johnson et al. 2015). Both partners of the couple completed daily journals to record lifestyle (e.g., smoking, sexual intercourse); female journals also queried about menses and pregnancy test results.

**Laboratory Analysis**

Persistent chemicals and blood metals were quantified at the Centers for Disease Control and Prevention using established standard operating procedures inclusive of quality assurance/quality control requirements. In total, 63 persistent chemicals/metals were measured in each partner: 1) polybrominated biphenyl #153; 2) nine organochlorine pesticides (OCPs) (i.e., hexachlorobenzene, beta-hexachlorocyclohexane, gamma-hexachlorocyclohexane, oxychlordane, trans-nonachlor, \( p,p^\prime \)-DDT, \( o,o^\prime \)-DDT, \( p,p^\prime \)-DDE, and mirex); 3) ten PBDEs (congeners #17, 28, 47, 66, 85, 99, 100, 153, 154, 183); 4) thirty-six 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, 209); and 4) seven PFASs (2-(N-ethyl-perfluorooctane sulfonamido) acetate, 2-(N-methyl-perfluorooctane sulfonamido) acetate, perfluorodecanoate, perfluorononanoate, perfluorooctane sulfonamide (PFOSA), perfluorooctane sulfonate, and perfluorooctanoate). Serum concentrations of OCPs, PBBs, PBDEs, and PCBs were measured using gas chromatography high-resolution mass spectrometry, and PFASs were measured using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (Kato et al. 2011; Kuklenyik et al. 2005; Sjödin et al 2004). Metals were quantified using inductively coupled plasma mass spectrometry. All POPs concentrations were reported in ng/g serum, while PFASs, cadmium and mercury were reported in ng/mL and in ug/dL.

Non-persistent chemicals were quantified at the Wadsworth Center using standard operating procedures. Total bisphenol A (BPA) and phthalate urinary concentrations were quantified (ng/mL) using HPLC-MS/MS (Zhang et al. 2011 and Guo et al. 2011, respectively). Fourteen phthalate metabolites were quantified: mono (3-carboxypropyl) phthalate (mCPP), monomethyl phthalate (mMP), monoethyl phthalate, mono (2-isobutyl phthalate), mono-\( n \)-butyl phthalate (mBP), mono (2-ethyl-5-carboxyphenyl) phthalate, mono-[(2-carboxymethyl) hexyl] phthalate, mono (2-ethyl-5-oxohexyl) phthalate, mono (2-ethyl-5-hydroxyhexyl) phthalate, monocyclohexyl phthalate, monobenzyl phthalate (mBzP), mono (2-ethylhexyl) phthalate, mono-isononyl phthalate, and monoocetyl phthalate (mOP). Five benzophenone-type ultraviolet light filter chemicals were quantified in urine using HPLC-MS/MS with established quality control procedures (Kunisue et al. 2010): 2,4-dihydroxybenzophenone (BP-1); 2,2′,4,4′-tetrahydroxybenzophenone (BP-2); 2-hydroxy-4-methoxybenzophenone (BP-3); 2,2′-dihydroxy-4-methoxybenzophenone (BP-8); and 4-hydroxybenzophenone (4OH-BP).

Serum cotinine was quantified using HPLC-MS/MS (Bernert et al. 1997), and serum lipids using commercially available enzymatic methods (Akins et al., 1989), and reported as total serum lipids (ng/g serum) (Phillips et al., 1989). Creatinine was quantified (mg/dL) using a Roche/Hitachi Model 912 clinical analyzer (Dallas, TX) and the Creatinine Plus Assay.
All instrument-derived concentrations that met quality control criteria (e.g., not instrument noise) were used for analysis without substituting concentrations below the limits of detection (LOD) or automatically lipid adjusting lipophilic chemicals to minimize bias when estimating human health outcomes (Richardson and Ciampi 2003; Schisterman et al. 2005, 2006).

Statistical analysis

We defined couple fecundity as TTP or the number of prospectively observed menstrual cycles required for couples to become pregnant. In published papers for each of the chemical classes and couple fecundity, we assessed the distributions of all chemicals by partner and relative to specific sociodemographic characteristics to aid in the specification of the models. We used Cox modeling techniques for discrete time (Cox 1972) and allowing for a cycle-varying intercept to estimate fecundability odds ratios (FORs) and 95% confidence intervals (CIs) for each chemical and the partner’s age accounting for the difference in couples’ ages. When the partners’ chemical concentrations were not highly correlated (i.e., benzophenones, metals, phthalates), we adjusted for the other partner’s chemical concentrations. Chemicals were log transformed and sometimes rescaled by their standard deviation depending upon chemical class. A priori established potential confounders were: age, body mass index (BMI, weight in kilograms/height in meter\(^2\)), serum cotinine to measure active smoking status (ng/mL; categorized as active (>100.0), passive (10.0-99.9), or no (<9.99) smoking); and research site (Michigan/Texas) to account for any residual confounding. For the benzophenone sunscreen chemical analysis, we also added season of enrollment (spring, summer, winter, fall). Serum lipids were included for the analysis of lipophilic chemicals and creatinine for chemicals measured in urine. Exact model specification is provided along with units for analysis in the footnote of Table 2. Couples were included in the analysis as censored upon withdrawal or if not pregnant after 12 months of trying. All testable modeling assumptions were evaluated. Diminished fecundity denotes FORs <1 or a longer TTP, while FORs >1 denote a shorter TTP. Consistent with our exploratory analytic plan, findings were considered significant if p-values were <0.05 or CIs excluded one without adjusting for multiple comparisons.

Results

Table 1 presents a comparison of the socio-demographic characteristics of participating couples by observed pregnancy status. One hundred (20%) couples withdrew from the study at some point while trying and did not have an observed pregnancy outcome, while 401 (80%) couples did including 347 (87%) that became pregnant and 54 (13%) who did not.

Table 2 summarizes the published partner specific results for various chemical classes. Male blood lead was associated with a 15% reduction in couple fecundity (Buck Louis et al. 2012), and similarly so for \( p,p' \)-DDE along with a range of 17%-29% reduction for 7 PCB congeners (Buck Louis et al. 2013). Three phthalates (mBP, mBzP, mMP) were associated with an 18%-23% reduction in fecundity based upon male partners (Buck Louis et al. 2014a), along with a 26% to 31% reduction for two BP-filters (BP-2 and 4OH-BP) (Buck Louis et al. 2014b). Of the 19 significant chemical findings in either partner found
associated with TTP, only 3 reflected higher fecundity as measured by a shorter TTP: male PCB congener #101 and female mCPP and mOP. Of note is the consistent pattern that male partners’ concentrations were more often associated with diminished fecundity than female partners’ concentrations. Only PCB congeners 167 and 209 were associated with diminished fecundity in both partners.

Models inclusive of both partners’ concentrations were run for heavy metals, BPA, BP-filters, and phthalates, given the low correlations between partners. Male partners’ concentrations of blood lead, BP-2, mBzP, and mMP remained significantly associated with diminished (ranging 17% to 31%) couple fecundity even after adjusting for female partners’ concentrations.

Discussion

As reviewed, the LIFE Study’s findings identify three important themes, all of which underscore the importance of considering the male partner for couple based outcomes like couple fecundity, as measured by TTP. First, male partners’ chemical concentrations were consistently more often associated with diminished couple fecundity than were female partners’ concentrations. In fact, only 2/86 (PCB congeners #167 and 209) chemicals assessed were consistently observed to be associated with diminished fecundity in both partners. As such, interpretation of the findings would be quite different if only one (not both) partner was studied. Second, 16/19 chemicals found to be significantly associated with couple fecundity were suggestive of diminished fecundity as evident by FORs <1. However, 3 chemicals (PCB congener #101 in males; mCPP and mOP in females) were positively associated with fecundity, reflecting in a shorter TTP. The third key finding is the consistency of male chemical concentrations being associated with diminished couple fecundity after adjusting for female partners’ concentrations. Collectively, the findings underscore the importance of measuring environmental chemicals in both partners of the couple when assessing couple-dependent outcomes such as TTP.

Interpreting the findings from the Life Study in the context of the available literature is challenging, given that much focuses on environmental chemicals and TTP relies exclusively on females. Our observed 17% reduction in couple fecundity in fully adjusted models associated with male blood lead concentrations is consistent with a previous report of a negative association between female blood lead and prospectively observed TTP in a cohort comprising 80 women (Bloom et al. 2011), and also with results from an occupational study that reported a dose-dependent relation with retrospectively recalled TTP (Shiau et al. 2004). In contrast, a cross-sectional sample of 41 pregnant couples reported no observed association between male partners’ lead concentration and TTP (Cole et al. 2006).

To our knowledge, there has been no prior work focusing on male POP concentrations and prospectively measured fecundity. Past research focusing on POPs and TPP has largely relied upon chemical concentrations in pregnant women who are asked to retrospectively report TTP with a few notable exceptions. A significantly longer retrospectively ascertained TTP was observed for PCB congener #153 and DDE concentrations among pregnant women but not their male partners from Greenland (Axmon et al. 2006). An earlier couple-based
preconception cohort assessed 8 PFCs in relation to prospectively measured TTP and reported no significant associations including for PFOSA (Vestergaard et al. 2012), as we observed in our study (Buck Louis et al. 2013).

In terms of non-persistent environmental chemicals and couple fecundity, again, we are unaware of any findings from previous preconception cohort studies with prospectively measured TTP for either one or both partners. One study compared 56 couples seeking infertility treatment with 56 couples with children and reported that specific urinary phthalates (DEP, DEHP, DnBP, BBzP) were higher in affected than unaffected couples (Tranfo et al. 2012), offering some support for the reduction in couple fecundity observed in the LIFE Study for male partner's mBzP concentration (Buck Louis et al. 2014a). Other evidence comes from prospective follow-up of couples undergoing assisted reproductive technologies such as the EARTH Study. Specifically, male partners’ urinary concentration of mCPP and mCOP were significantly associated with both a lower odds of implantation and live birth, whereas monobutyl was only associated with a lower odds of a live birth (Dodge et al. 2015). These phthalates were suggestive of diminished fecundity in the LIFE Study as measured by FORs <1.0, but the findings were not significant. Bisphenol A was not associated with a range of IVF outcomes in the EARTH Study (Minguez-Alarcón et al. 2015), similar to the absence of an association in the LIFE Study (Buck Louis et al. 2014a).

And finally relative to benzophenone chemicals such as those used in sunscreen products, we found only one other study that looked at BP-3 and semen quality endpoints. No significant trend in BP-3 concentrations and semen quality parameters was observed, nor was there an association with BPA (Chen et al. 2013). Neither BP-3 nor BPA was associated with couple fecundity in the LIFE Study (Buck Louis et al. 2014a, 2014b). We are unaware of any previous research on BP-2 or 4OH-BP found to be associated with TTP in our study.

Our findings that specific exposures within various chemical classes may be associated with diminished couple fecundity support continued investigation of environmental exposures, inclusive of endocrine disrupting chemicals (EDCs). Previous reviews focusing more globally than couple fecundity on EDCs and male reproductive health (Pfieger-Bruss et al 2004; Bergman et al. 2012) underscore the need for continued study, especially with respect to timing of exposure, sex specific differences and possible trans-generational effects (Gore et al. 2015). Recently estimates of population impact and cost of EDCs on male reproductive health suggest that phthalates alone may be responsible for 618,000 additional assisted reproductive technology procedures resulting in an estimated €4.71 billion annually for the European Union (Hauser et al. 2015). These same authors concluded that EDCs over a male's life course contribute to a spectrum of reproductive disorders ranging from genital-urinary malformations, altered hormonal profiles, infertility, to testicular cancer. With an estimated infertility prevalence of 12% as reported by a representative sample of reproductive aged U.S. men (Louis et al. 2013), the implications of fecundity related impairments for men's health is notable.

Many of the findings described in this paper suggest that specific EDCs may be associated with diminished fecundity, consistent with some earlier findings from experimental animal and, to a lesser extent, human evidence focusing on reproductive health, as summarized in

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scientific statements (Hotchkiss et al. 2008; Diamanti-Kandarakis et al. 2009) or recent reviews (Mathur and D'Cruz 2011; Wan et al. 2013). From these publications and other original work, there is concern that males may be more susceptible to EDCs than females in light of their early life sexual differentiation being androgen-dependent. The second consideration is the importance of timing of exposure given increasing recognition that peri-conception or in utero exposures may have lifelong effects on human fecundity and fertility. Underlying etiologic mechanisms remain largely unknown, possibly a function of EDCs having many modes of action beyond the mimicking of estrogens and/or antagonizing androgens. The diverse modes of action are posited to not only adversely affect spermatogenesis, steroidogenesis or the functioning of Sertoli and Leydig cells, but may be expanded to include nuclear as well as steroid and non-steroid receptors and enzymatic pathways (Diamanti-Kandarakis et al. 2009). Other mechanistic research has demonstrated the ability of EDCs to induce reactive oxygen species resulting in oxidative stress within the testes (Mathur and D'Cruz, 2011). In light of the limited data on human populations and cross-species differences, caution is needed when weighing animal and human evidence in light of reported differences between humans and rodents in terms of EDC threshold susceptibilities in fetal testes (Habert et al. 2014).

There are many remaining challenges when attempting to delineate the impact of EDCs on human fecundity, including recognition that TTP is a functional measure of couple fecundity. Longer TTP does not readily identify if it is the result of changes in hormonal profiles, semen quality and/or ovulation or menstruation. The LIFE Study team is currently undertaking research aimed at determining whether EDCs adversely impact semen quality, which in turns results in a longer TTP or pregnancy loss. In addition, we are planning to use banked semen samples for the quantification of chemicals and basic mechanistic research aimed at assessing potential underlying mechanisms.

Other remaining challenges for answering lingering data gaps regarding EDCs and human fecundity and fertility include the need for prospective couple based cohorts to capture exposures over critical windows of human reproduction and development, and assessment of later onset adult health risks and possible trans-generational effects. Analytic methods for even greater laboratory detection of existing and emerging compounds will help to minimize measurement error, while evolving statistical methodologies will better accommodate the hierarchical data structure for studying couples and in deciphering chemical signatures from complicated chemical and lifestyle mixtures. Simultaneous mechanistic work grounded within such cohorts will facilitate the delineation of mechanisms that might provide an opportunity for intervention.

Acknowledgement

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References


Table 1
Comparison of couples by observed pregnancy status, LIFE Study (n=501).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnant (n=347) n (%)</th>
<th>Not Pregnant (n=54) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female Partner</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>285 (82)</td>
<td>39 (72)</td>
</tr>
<tr>
<td>College education</td>
<td>331 (95)</td>
<td>52 (96)</td>
</tr>
<tr>
<td>Health insurance</td>
<td>332 (96)</td>
<td>49 (91)</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>29.8 (3.9)</td>
<td>30.6 (4.3)</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>27.0 (6.7)</td>
<td>28.7 (9.1)</td>
</tr>
<tr>
<td><strong>Male Partner</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White non-Hispanic</td>
<td>278 (80)</td>
<td>42 (78)</td>
</tr>
<tr>
<td>College education</td>
<td>328 (95)</td>
<td>49 (91)</td>
</tr>
<tr>
<td>Health insurance</td>
<td>326 (94)</td>
<td>47 (87)</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>31.6 (4.6)</td>
<td>32.4 (5.3)</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>29.7 (5.5)</td>
<td>30.3 (5.5)</td>
</tr>
</tbody>
</table>

NOTE: 100 (20%) couples withdrew at some point while trying and before an observed pregnancy.
Table 2

Summary of fecundability odds ratios for persistent and non-persistent environmental chemicals by partner, LIFE Study.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Female Partner FOR (95% CI)</th>
<th>Male Partner FOR (95% CI)</th>
<th>Female Partner Adjusting for Male FOR (95% CI)</th>
<th>Male Partner Adjusting for Female FOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Persistent Metals &amp; Chemicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy metals&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium (ug/L)</td>
<td>0.78 (0.63, 0.97)</td>
<td>0.85 (0.71, 1.02)</td>
<td>0.81 (0.64, 1.02)</td>
<td>0.93 (0.78, 1.12)</td>
</tr>
<tr>
<td>Lead (ug/dL)</td>
<td>0.97 (0.85, 1.11)</td>
<td>0.85 (0.73, 0.98)</td>
<td>1.05 (0.91, 1.23)</td>
<td>0.83 (0.70, 0.98)</td>
</tr>
</tbody>
</table>

**Persistent organic pollutants (ng/g serum)<sup>b</sup>**

| OCPs | | | | |
| p,p′-DDE | 0.83 (0.70, 0.97) | -- | -- | |

| PCB congeners | | | | |
| 101 | 1.26 (1.09, 1.51) | -- | -- | |
| 118 | 0.82 (0.68, 0.98) | -- | -- | |
| 138 | 0.71 (0.52, 0.98) | -- | -- | |

| 156<sup>c</sup> | 0.77 (0.62, 0.96) | -- | -- | |
| 157<sup>c</sup> | 0.83 (0.70, 0.97) | -- | -- | |
| 167<sup>c</sup> | 0.79 (0.64, 0.97) | 0.82 (0.70, 0.96) | -- | -- |
| 170 | 0.74 (0.56, 0.98) | -- | -- | |
| 172 | 0.82 (0.68, 0.99) | -- | -- | |
| 209 | 0.82 (0.68, 0.99) | 0.78 (0.65, 0.94) | -- | -- |

**PFOSA (ng/mL)** | 0.82 (0.71, 0.95) | -- | -- |

**Non-persistent Chemicals**

| Phthalates<sup>c</sup> | | | | |
| mBP | 0.93 (0.77, 1.12) | 0.82 (0.70, 0.97) | 0.95 (0.78, 1.16) | 0.87 (0.73, 1.04) |
| mBzP | 0.94 (0.79, 1.13) | 0.77 (0.65, 0.92) | 0.98 (0.81, 1.20) | 0.80 (0.67, 0.97) |
| mCPP | 1.20 (1.00, 1.43) | 0.96 (0.85, 1.13) | 1.22 (1.02, 1.47) | 0.97 (0.83, 1.12) |
| mMP | 0.93 (0.81, 1.08) | 0.80 (0.70, 0.93) | 0.99 (0.85, 1.15) | 0.81 (0.70, 0.94) |
| mOP | 1.09 (0.96, 1.23) | 0.99 (0.87, 1.12) | 1.18 (1.03, 1.35) | 0.92 (0.80, 1.06) |

| Benzenophenone-type UV filters<sup>d</sup> | | | | |
| BP-2 | 0.82 (0.60, 1.12) | 0.69 (0.50, 0.95) | 0.89 (0.64, 1.24) | 0.69 (0.49, 0.97) |
| 4OH-BP | 0.77 (0.56, 1.06) | 0.74 (0.54, 1.00) | 1.20 (0.83, 1.71) | 1.11 (0.77, 1.60) |

NOTE: Results are restricted to those chemicals observed to be significantly associated with fecundability in either or both partners. Separate models were run for each chemical and partner. Significant (p<0.05) fecundability odds ratios (FORs) and 95% confidence intervals (CIs) are in boldface. Estimates were rounded to two decimal places.

<sup>a</sup> Adjusted for age (years); body mass index (kg m<sup>−2</sup>) categorized as underweight (<18.5), normal (18.5-24.9), overweight (25.0-29.9), and obese (30.0-34.9); research site (Texas/Michigan); couples’ serum cotinine concentrations (ng/mL) categorized as active (≥100.0), passive (10.0-99.9), or

Andrology. Author manuscript; available in PMC 2017 July 01.
no (<9.99) smoking); serum lipids (ng/g serum, continuous); and parity (nulliparous/parous), then adjusting for the other partner's metal concentrations, differences in couples' ages (years, continuous) and accounting for time couples were off contraception prior to recruitment. All metals were rescaled by their standard deviation for analysis. See Buck Louis et al. 2012 for complete details.

Adjusted for age (≤27 vs. >27 years for females and ≤28 vs. >28 years for males); BMI (continuous); serum cotinine (ng/mL continuous); serum lipids (ng/g serum left continuous but not included in the model for non-lipophilic chemical PFOSA); research site (Texas or Michigan); and the sum of remaining chemicals within a class while accounting for time couples were off contraception prior to enrollment. Chemical concentrations were log transformed and rescaled by their standard deviation for analysis. See Buck Louis et al. 2013 for complete details.

Adjusted for age (years); BMI (continuous); serum cotinine (ng/mL continuous); urinary creatinine (mg/dL continuous); and research site (Texas/Michigan) then adjusting for the other partner's chemical concentrations, difference in couples' ages (years) and accounting for time couples were off contraception prior to enrollment. Chemicals concentrations were log transformed and rescaled by their standard deviations for analysis. See Buck Louis et al. 2014a for complete details.

Adjusted for age (years); BMI (under/normal weight (<24.9), overweight (25.0-29.9), obese ≥30.0); serum cotinine (ng/mL categorized as active (>100.0), passive (10.0-99.9) or no (<9.99) smoking); creatinine concentrations (mg/dL continuous), research site (Michigan/Texas); and season (winter, spring, summer, fall) of enrollment, then adjusting for the other partner's BP-type filter concentration, difference in couples' ages (years) and accounting for time off contraception prior to recruitment. Chemical concentrations were dichotomized at/above versus below the 75th percentile for analysis. See Buck Louis et al. 2014b for complete details.

Dioxin-like PCB congeners