Published in final edited form as:
Reproduction. 2014 ; 147(4): R97–R104. doi:10.1530/REP-13-0472.

Persistent Environmental Pollutants and Couple Fecundity: An Overview

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Abstract

Speculation has arisen that human fecundity may be declining, possibly a function of exposure to persistent environmental chemicals that resist degradation resulting in various pathways for human exposure. In contrast to considerable animal evidence suggesting adverse effects of such chemicals on reproduction, limited human research has been undertaken. To date, available data stem largely from 10 unique study cohorts that have quantified individual chemical exposures in relation to time-to-pregnancy (TTP), which is a measure of couple fecundity. Diminished fecundability odds ratios (FORs) indicative of longer TTP were observed in all but two studies, though not all findings achieved statistical significance. Persistent chemicals associated with reduced couple fecundity as measured by a longer TTP included β-HCH, cadmium, lead, mercury, *p,p'*-DDE, TCCD dioxin, and select PBDEs, PCBs and PFCs. Important methodologic limitations need to be considered in weighing the evidence: 1) reliance on pregnant women, which may exclude women with the highest exposures if related to the inability to conceive; 2) retrospectively reported TTP, which may be associated with bi-directional reporting errors and 3) limited attention to male partners or couples' exposures. While current evidence is not inconsistent with animal evidence, concerted efforts to address lingering data gaps should include novel strategies for recruiting couples, the longitudinal measurement of TTP and the continued enrollment of couples across successive pregnancies. This latter strategy will provide a more complete understanding of the toxicokinetics of chemicals during sensitive windows and their implications for fecundity and its related impairments.

Introduction

An evolving body of evidence suggests that human fecundity, defined as the biologic capacity of men and women for reproduction irrespective of pregnancy intentions (Buck Louis 2011a), may be declining raising concerns about the sustainability of some populations (Daguet 2002; Lutz et al. 2003; Skakkebaek et al. 2006). While controversial in many regards, evidence consistent with diminishing male fecundity includes declining semen quality reported by some authors (Zou et al. 2011; Geoffroy-Siraudin et al. 2012) but not all as recently summarized (Fisch and Braun 2013), along with higher genital-urinary malformation rates among men with fecundity impairments or reproductive site cancers in comparison to unaffected individuals (Bray et al. 2006; Skakkebaek et al. 2006, 2007;

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Declaration of Interest
The author declares no known or possible conflicts with the sponsors of the COW meeting.

This article is based on work presented at the 7th Copenhagen Workshop on Endocrine Disrupters, which was supported by the Danish Ministry of the Environment – Environmental Protection Agency.

Saravelos et al. 2008). The relatively high prevalence rates of fibroids, polycystic ovarian syndrome and endometriosis (Baird et al., 2003; Azziz et al. 2004; Gylfason et al. 2010) may be suggestive of diminishing female fecundity, while increasing infertility rates may be indicative of diminished couple fecundity (Priskorn et al. 2012; Thoma et al. 2013).

Fecundity is now recognized to have implications across the lifespan. For example, boys born with genital-urinary malformations are at increased risk of alterations in semen quality, infertility and testes cancer in adulthood than unaffected boys (Trussell and Lee 2004; Bray et al. 2006). In fact, recent authors have reported semen quality to be positively associated with longevity (Jensen et al. 2009). Associations between female fecundity and later onset disease also have been reported. For example, girls born small-for-gestation are reported to have poorer adult ovarian development and function relative to adequately sized girls (Ibáñez et al 2000). Girls with low birth weights irrespective of gestation were reported to have biochemical and clinical features characteristic of polycystic ovarian syndrome (Pandolfi et al. 2008). Similarly, women with polycystic ovaries are at increased risk of gravid disease and metabolic disorders later in adulthood (Talbott et al. 2004). Infertility also was observed to be associated with gravid diseases such as gestational diabetes (Tobias et al. 2013). Collectively, the findings in males and, subsequently, females have been conceptualized as suggesting an early origin for onset, or the so-called testicular and ovarian dysgenesis syndromes (Skakkebaek et al. 2001; Buck Louis et al. 2011b).

Potential reasons for declining fecundity are largely unexplored, though environmental factors are suggested and serve as the impetus for this paper. Attention is directed to persistent chemicals that resist degradation, as indicative by their long half-lives spanning several years for some compounds [ww.cdc.gov/exposurereport/pdf/FourthReport.pdf]. Such chemicals include: 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) and its parent compound 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT); dioxin; metals; organochlorine pesticides (OCPs); polybrominated biphenysl (PBBs); polybrominated diethers (PBDEs), polychlorinated biphenyls (PCBs), and perfluorochemicals (PFCs). This paper is organized as three questions and concludes with a summary of chemicals reported to adversely affect fecundity using a weight of evidence approach.

How can couple fecundity be assessed relative to environmental chemicals?

A range of possible outcomes can be used to assess either male or female fecundity when considered individually. In contrast, couple fecundity is largely measured by time-to-pregnancy (TTP), which is defined as the number of menstrual cycles or calendar months required to become pregnant. TTP is used globally as a marker of how quickly a couple becomes pregnant, or not. It can also be categorized to denote fecundity related impairments such as conception delay (TTP >6 cycles/months) or infertility (>12 cycles/months) recognizing that neither of these two impairments denotes sterility without further medical investigation.

In prospectively followed couples attempting pregnancy, approximately 80% of women achieve pregnancy within 6 cycles of trying (Bonde et al. 1998; Buck Louis et al. 2011c), while 13% – 18% of couples do not achieve pregnancy within 12 months (Zinaman et al. 1996; Buck Louis et al. 2012). Of note are the regional differences in TTP (Juul et al. 1999; Sanin et al. 2009). The extent to which such differences in TTP reflect regional variations in semen quality (Jørgensen et al. 2001; Punab et al. 2002; Swan et al. 2003) remains to be established.

One important limitation of using TTP as a measure of couple fecundity is that it provides no information as to whether the delays are male, female or couple mediated. Much of the available research relies upon females not couples. A second data gap is the absence of research that has empirically assessed how male (e.g., semen quality) and female (e.g., ovulatory cycles) fecundity jointly mediates couple fecundity or TTP. This data gap likely reflects the few prospective cohort studies with preconception enrollment of couples conducted to date (Buck Louis et al. 2004).

While TTP can be estimated with the use of prospective and retrospective designs, the former is considered the gold standard given its ability to longitudinally measure at risk time and incident pregnancy along with other time-varying lifestyle factors such as alcohol consumption or smoking. While reliability is reported to be good for retrospectively measured TTP even after long period of recall (Joffe et al. 1993), its validity is only good for short recall or within 3–20 months (Zielhuis et al. 1992). However, it has poor validity for longer periods of recall as reflected in bidirectional errors or the under- and over-reporting of TTP by women (Cooney et al. 2009). Another important methodologic limitations underlying the use of retrospective TTP is digit preference reporting (Ridout and Morgan 1991).

The fecundability odds ratio (FOR) estimates the probability of pregnancy each menstrual cycle or month, given exposure and conditional on not having achieved pregnancy in the previous cycle. FORs are estimated along with their 95% confidence interval (CI) for assessing significance. A FOR <1.0 denotes reduced fecundability or a longer TTP, whereas an FOR >1.0 denotes enhanced fecundability or a shorter TTP. Despite increasing recognition of the importance of lifestyle factors for TTP (Rothman et al. 2013), only 14% of the variation in TTP was explained by oral contraceptive use, cycle length, age, and parity at the population level, whereas other lifestyle factors were not retained in models (Axmon et al. 2006a). This finding underscores our limited understanding of the population and individual level determinants of human fecundity, and is an important consideration when assessing environmental chemicals.

What research has focused on persistent chemicals and couple fecundity?

Research relying on retrospectively collected TTP—Very little research has focused on persistent environmental chemicals and couple fecundity, despite many such compounds having been quantified in semen, follicular and genital track fluid (Wagner et al. 1990; DeFelip et al. 2004; Jirsová et al. 2010). To date, much the available research relies upon retrospectively ascertained TTP from pregnant women or women with unique residential or lifestyle (i.e., fish consumption) exposures. Axmon and colleagues (2004) queried 183 sisters of fishermen about TTP and obtained a blood sample for the quantification of plasma PCB conger 153 approximately 20 years following the first planned pregnancy necessitating the need to backwardly extrapolate exposure at the relevant time period for TTP. A positive association was observed suggesting enhanced fecundity or a shorter TTP, including for another subset of wives of fisherman. The findings, however, did not achieve significance. In a subsequent study, Axmon and colleagues (2006b) recruited pregnant women and their male spouses from Greenland, Kharkiv and Warsaw and queried them about TTP. FORs <1.0 were observed for male and female serum PCB 153 for Greenland and Kharkiv but not Warsaw, and female DDE concentrations also was associated with FORs <1.0 but only in Greenland. However, only the findings for female exposures in Greenland achieved significance. Gesink Law and colleagues (2005) utilized the historic U.S. Collaborative Perinatal Project that enrolled pregnant women from 12 clinical sites in the U.S., 1959–1965. Banked serum was analyzed for 390 women for the quantification of 11 PCBs, DDT and DDE. Women in the highest quintile of PCBs and DDE

had a ≈35% reduction in fecundity or a longer TTP when compared to women in the lowest categories. However, the findings failed to reach significance.

Harley and colleagues (2008) assessed serum DDT and DDE concentrations in 289 pregnant migrant farmworkers participating in the CHAMACOS Cohort Study in relation to retrospectively collected TTP. FORs were all below one, reflecting reduced (2% to 9%) fecundity for *o, p′*-DDT, *p, p′*-DDT, and *p, p′*-DDE, respectively. Subsequently, Harley and colleagues (2010) assessed 10 serum PBDE congeners for a subset of pregnant women in the CHAMACOS Cohort. Only PBDE congener 100 was associated with a significant 40% reduction in fecundity, with findings robust to additional sensitivity analyses given their reliance on retrospective TTP.

Cole and colleagues (2006) utilized a cross-sectional design to quantify OCPs, PCBs and metals in 41 first time pregnant couples. Only female blood mercury was associated with reduced fecundity, conferring a 78% significant reduction in fecundity. Dioxin and TTP has been assessed in one study. Specifically, Eskenazi and colleagues (2010) assessed serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) concentrations in 278 women that were extrapolated back to the time women were attempting pregnancy following a dioxin plant explosion in relation to retrospectively reported TTP for 278 (28%) women. Fecundity was reduced ≈25%, and a twofold higher odds of infertility or achieving pregnancy after 12+ months of trying also was observed for participants.

With regard to PFCs, Fei and colleagues (2009) utilized banked biospecimens for the quantification of plasma perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations among a subset of 1,240 pregnant women who participated in the Danish National Birth Cohort and who were queried about TTP during pregnancy. Significant inverse trends were observed for both PFOA and PFOS and TTP, reflecting an approximate 30% reduction in fecundity for women in the highest three quartiles relative to women in the lowest.

Two other pregnancy studies are worth mentioning despite not being directly comparable to research with individual chemical concentrations and TTP. Whitworth and colleagues (2012) assessed plasma PFOA and PFOS concentrations in 910 pregnant women participating in the Norwegian Mother and Child (MoBA) Cohort Study with retrospectively collected TTP dichotomized as requiring >12 months for pregnancy versus ≤12 months. Parous but not nulliparous women in the highest quartiles of PFOA and PFOS had a significant twofold higher odds of a TTP >12 months in comparison to women with lower concentrations. In the PELAGIE Cohort, pregnant mothers were queried about their TTP in relation to 14 OCPs, 12 PCBs and 10 PBDEs that were quantified in the cord blood of 394 infants (Chevrier et al. 2013). Negative associations were observed for most compounds, particularly for total PCBs (54% reduction), *p,p′*-DDE (40% reduction) and two OCPs (βHCH and HCB 39% and 10%, respectively).

Research with prospectively measured TTP—Two prospective cohort studies with preconception enrollment of women have assessed PCBs and PFCs. Buck Louis and colleagues (2009) recruited 83 women upon discontinuing contraception with daily follow-up through 12 menstrual cycles at risk for pregnancy in the New York State Angler Cohort Study (NYSACS). Both estrogenic and anti-estrogenic PCBs were associated with ≈68% reduction or more in fecundity, though the findings did not achieve significance. A second prospective cohort study with preconception recruitment of couples followed for six months reported by Vestergaard and colleagues (2012) utilized banked serum from 222 women who participated in the Danish First-Pregnancy Planners Cohort, 1992–1995 (Bonde et al. 1998). Of the 8 PFCs considered, two metabolites - EtFOSAA and MeFOSS - conferred FORs <1.0

reflecting a 20% and 10% reduction, respectively. However, the findings did not achieve significance.

The most recently conducted prospective cohort study with preconception enrollment of both partners of the couple for the specific investigation of environmental influences on human fecundity is the Longitudinal Investigation of Fertility and the Environment (LIFE) Study (Buck Louis et al. 2011c). Couples were recruited from targeted geographic areas with reported exposures to persistent compounds upon discontinuing contraception. TTP was longitudinally measured using a combination of data from the daily journals completed by both partners and the Clearblue™ Fertility Monitor, which provided visual prompts to help couples time intercourse relative to ovulation.

Pregnancy denoted a positive home pregnancy test on the day of expected menstruation using digital home test kits. Various environmental compounds were associated with diminished fecundity, and surprising few were associated with enhanced fecundity as measured by FORS >1. Specifically, female blood cadmium and male lead concentrations were associated with a 22% and 15% reduction in fecundity, respectively, when modeled individually (Buck Louis et al. 2012). When both partners' blood metals were jointly modeled given the low correlation between partners, male lead concentration continued to reflect an 18% reduction in fecundity. All findings remained significant even after adjusting for relevant covariates. Also, female serum concentrations of PCB congeners 118, 167 and 209 and perfluorooctane sulfonamide (PFOSA) were consistently associated with diminished fecundity, ranging from 18% to 21% (Buck Louis et al. 2013). Among male partners, *p,p'*-DDE and PCB congeners 138, 156, 157, 167, 170, 172, and 209 were significantly associated with reduced (17% to 29%) fecundity denoting a longer TTP. Male partners' concentration of PCB 101 was the only chemical significantly associated with enhanced fecundity or a shorter TTP.

Table 1 summarizes the weight of evidence reported by ten different study cohorts that had individual chemical measurements and data on either retrospective or prospective TTP data. This summary table reflects the sparse available data, and a preponderance of data relying on pregnant women, retrospective TTP and the limited attention to male partners. Despite these challenges, all but two studies reported FORs <1.0 for at least one chemical suggesting an association with diminished couple fecundity. However, not all the findings achieved significance. Findings from the LIFE Study corroborate earlier reports, including for female PCBs concentrations (Axmon et al. 2006), *p,p'*-DDE (Harley et al. 2008) when based upon male concentrations, and PFOS and PFOSA (Fei et al. 2009). Of note is the observation that the magnitude of FORs reported for various persistent chemicals is relatively smaller than those reported for biologic determinants such as oligospermia or gynecologic disorders (i.e., FORs 0.34 and 0.46, respectively (Vestergaard et al. 2012), but comparable for those reported for cigarette smoking or serum cotinine concentrations, higher body mass indices and parental ages (Buck Louis et al. 2012; Chevrier et al. 2013).

What are the next steps for answering data gaps?

Globally, two avenues of research may offer insight regarding the relation between environmental chemicals and couple fecundity. One avenue is to continue to leverage existing pregnancy or birth cohort studies. A number of recent pregnancy cohort studies have been implemented in the past decade, and most have banked biospecimens that may be suitable for continued investigation. Still, such effort will be limited by reliance on women successfully achieving pregnancy and retrospective TTP. If exposures prevent couples from achieving pregnancy, they will be excluded from the study cohort and possibly impact study conclusions. Still it may be possible to devise strategies to measure exposures of women not

achieving pregnancy to empirically assess this lingering question, and to foster data driven decision-making. A second promising avenue is to leverage children form existing birth cohorts and to design prospective TTP studies when they enter reproductive years. This approach will provide information on the woman's *in utero* exposure and also her exposure at the time she is interested in becoming pregnant. The same would be true for males. Ideally, it would be important to follow couples through all their pregnancy trying attempts to obtain data relevant for understanding the toxicokinetics of chemicals and their impact on sensitive fecundity endpoints across successive pregnancy attempts. Such an approach would be highly informative for the proper modeling of exposures and reproductive outcomes in the context of a couple's past reproductive performance (e.g., parity) and other relevant factors such as age. Irrespective of approach or any others that may be relevant, every effort should be made to quantify exposures in both partners in keeping with the couple dependent nature of human reproduction. Failure to consider male partners may result in erroneous conclusions when based solely on female exposures.

With increased recognition of the need to model chemical mixtures in keeping with the nature of human exposure, continual efforts to develop statistical models for handling correlated and hierarchical data characteristic of couple based designs are urgently needed. This work becomes more challenging when attempting to include lifestyle and diet to identify potential modifying factors that may minimize the effects stemming from internal chemical doses and, thereby, promote health and well being. While beyond the focus of this paper, future work also should include measurement of both persistent and non-persistent chemicals, given the growing evidence suggesting an adverse relation between short-lived compounds such as bisphenol A and phthalates and a spectrum of reproductive endpoints. Adverse effects reported include alterations in hormonal milieu, reduced number of oocytes retrieved and implanted among couples undergoing assisted reproductive technologies and alterations in semen quality (Duty et al. 2003; Jönsson et al. 2005; Mendiola et al. 2010; Mok-Lin et al. 2010; Ehrlich et al. 2012). Perhaps, efforts such as environmental wide association studies (EWAS) may be one approach for considering all environmental chemicals, but others options are likely to emerge in the near future. Continued efforts also are needed to resolve lingering laboratory analytical issues, such as the ideal modeling of chemical concentrations below the laboratory limits of detection or alternatives to the automatic adjustment of chemicals for serum lipids or urinary creatinine when assessing potential reproductive toxicity.

Conclusion

An evolving body of observational research suggests that environmentally relevant concentrations of select persistent environmental chemicals may be affecting human fecundity, as evident as a longer time required for achieving pregnancy. Such subtle changes may easily be missed without continued and purposeful research aimed at the preconception enrollment of *couples* for longitudinal measurement of sensitive outcomes such as TTP and pregnancy loss. Male mediated exposures also are important and failure to consider them when assessing couple dependent outcomes such as TTP or pregnancy loss may result in erroneous conclusions, particularly in the absence of female exposures. Future research will require sophisticated analytic methods that are well grounded within human biology and capable of handling the hierarchical and correlated structure of chemical exposures as we seek to delineate and quantify threats to human fecundity. In the context of emerging chemical signals potentially relevant for human fecundity, this author urges shared collaboration and creative utilization of existing resources from which to answer lingering data gaps. The excellent work reported above that utilized banked biospecimens from pregnancy cohort studies is a step in the right direction, but cannot replace the need for prospective cohort studies with preconception enrollment of couples. Novel strategies aimed

at recruiting contemporary birth cohorts who are or will be soon testing their fecundity are needed. Such empirical evidence is needed for informing public policy and informed decision-making.

Acknowledgments

Funding

Supported by the Intramural Research Program of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Funding for the LIFE Study was provided by contracts N01-HD-3-3355; N01-HD-3-3356; NOH-HD-3-3358.

Publication of this special issue was supported by the Society for Reproduction and Fertility.

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Table 1

Summary of literature regarding persistent environmental chemicals and couple fecundity, as measured by time-to-pregnancy.

Author & Year	Study Cohort or Sample	Media and Chemical(s)	TTP	FORs & Significance
Axmon et al. 2004	165 sisters & 121 wives from the Swedish Fisherman Study	Serum for sisters after pregnancy* Plasma for wives after pregnancy* PCB 153	Retrospective (≈20 years)	↑ FORs 1.27–1.42; not significant
Axmon et al. 2006	1,505 pregnant women & 778 male partners from 4 countries (Greenland, Kharkiv, Sweden, Warsaw)	Serum collected in pregnancy PCB 153 *p,p'*-DDE	Retrospective	↓ FORs 0.68–0.75; significant for females in Greenland
Gesink Law et al. 2005	390 pregnant women from U.S. Collaborative Perinatal Project	Serum during pregnancy 11 PCBs, DDT, DDE	Retrospective	↓ FORs 0.65–1.03; not significant
Cole et al. 2006	41 pregnant female & male partners	Blood & plasma during pregnancy OCPs, PCBs Mercury & lead	Retrospective	↓ FOR 0.22–0.30; significant for female mercury & benzene hexachloride; FOR 0.27; significant for male PCBs
Harley et al. 2008	289 pregnant women from CHAMACOS Cohort Study	Serum during pregnancy *p,p'*-DDT, *o,p'*-DDT, *p,p'*-DDE	Retrospective	↓ FOR 0.91–0.98; not significant
Buck Louis et al. 2009	83 women recruited preconception & longitudinally followed, New York State Angler Cohort Study	Serum when trying for pregnancy 76 PCBs	Prospective	↓ FORs 0.01–0.32; not significant
Fei et al. 2009	Subset 1,240 women from Danish National Birth Cohort	Plasma during pregnancy PFOS, PFOA	Retrospective	↓ FORs 0.70–0.72; significant
Eskenazi et al. 2010	278 women attempting pregnancy after Seveso explosion	Serum after pregnancy* TCCD dioxin	Retrospective	↓ FOR 0.73–0.75; significant
Harley et al. 2010	Subset of 223 pregnant women from CHAMACOS Cohort Study	Serum during pregnancy PBDEs	Retrospective	↓ FORs 0.34–0.58; significant
Buck Louis et al. 2012	501 couples recruited prior to conception & followed for 12 months of trying, LIFE Study	Blood when trying for pregnancy Cadmium, lead, mercury	Prospective	↓ FOR 0.78; significant for female cadmium. FOR 0.85; significant for male lead.
Vestergaard et al. 2012	22 women recruited prior to conception & followed for 6 cycles of trying	Serum when trying for pregnancy 8 PFCs	Prospective	↑ FOR 0.79–1.39; not significant
Chevrier et al. 2013	Subset of 332 women from the PELAGIE Cohort with cord blood	Cord Blood 14 OCPs, 10 PBDEs, 12 PCBs	Retrospective	↓ FORs 0.37– 0.64; significant DDE, βHCH, PCBs
Buck Louis et al. 2013	501 couples recruited prior to conception & followed for 12 months of trying, LIFE Study	Serum when trying for pregnancy 9 OCPs, 1 PBB, 10 PBDEs, 36 PCBs, 7 PFCs	Prospective	↓ FORs 0.79–0.82; significant for PCBs & PFOSA. FORs 0.71–0.83; significant for male *p,p'*-DDE & PCBs.

NOTE: Literature restricted to research that assessed individual chemical concentrations in relation to time-to-pregnancy (TTP) as quantified by fecundability odds ratios (FORs) for assessing couple fecundity.

*Exposures were back extrapolated to relevant time-to-pregnancy interval using various methods.

↑ denotes FORs >1.0 or a shorter time-to-pregnancy; ↓ denotes FORs <1.0 or a longer time-to-pregnancy