Curr Epidemiol Rep (2016) 3:39–50
DOI 10.1007/s40471-016-0060-1

REPRODUCTIVE AND PERINATAL EPIDEMIOLOGY (EF SCHISTERMAN AND E YEUNG, SECTION EDITORS)

Female Infertility and "Emerging" Organic Pollutants of Concern

Michael S. Bloom[1,2,3] · **Romeo Micu**[4] · **Iulia Neamtiu**[3,5]

Published online: 1 February 2016

Abstract Modern chemical instrumentation has fostered a revolution of sorts, in which epidemiologic studies of female infertility can now devote attention to very low level, "background" exposures to "emerging" non-persistent organic pollutants, rather than on "legacy" persistent organic pollutants. Predicated on widespread and frequent contact, and substantial experimental evidence of estrogen-disruptive effects, concern for phthalate diesters, environmental phenols (bisphenol A and triclosan), and ultraviolet filters (benzophenones) as risk factors for female infertility has grown. We reviewed the contemporary epidemiologic evidence for these emerging environmental pollutants as risk factors for female infertility. We conclude that the epidemiologic evidence is insufficient to date, to substantiate background exposures as risk factors for female infertility. However, very few epidemiologic investigations have been published. To more definitively address concerns, additional epidemiologic investigations are needed, including longitudinal collection of multiple biospecimens, simultaneous consideration of couple-level exposures, and incorporating mixtures of these and additional emerging organic pollutants.

Keywords Endocrine disruptors · Environmental estrogens · Female infertility · Phenols · Phthalates · UV filters

Introduction

Female Infertility

Recently, the International Federation of Gynecology and Obstetrics (FIGO) joined with the American College of Obstetrics and Gynecology (ACOG), the American Society for Reproductive Medicine (ASERM), and the Endocrine Society in calling for greater attention to the impacts of environmental pollutants on human reproductive health [1•, 2•, 3]. Hundreds of chemicals, including environmental pollutants, behave as "endocrine disruptors" in vitro or in vivo, acting

This article is part of the Topical Collection on *Reproductive and Perinatal Epidemiology*

✉ Michael S. Bloom
mbloom@albany.edu

Romeo Micu
romeomicu@hotmail.com

Iulia Neamtiu
iulianeamtu@ehc.ro

[1] Department of Environmental Health Sciences, School of Public Health, University at Albany, State University of New York, One University Place, Rm. #157, Rensselaer, NY 12144, USA

[2] Department Epidemiology and Biostatistics, School of Public Health, University at Albany, State University of New York, One University Place, Rm. #157, Rensselaer, NY 12144, USA

[3] Environmental Health Center, Str. Busuiocului, Nr. 58, Cluj-Napoca 400240, Romania

[4] Assisted Reproduction Department, Gynecology I Clinic, University of Medicine and Pharmacy "Iuliu Haţieganu", Str. Clinicilor, Nr. 3-5, Cluj-Napoca 400006, Romania

[5] IMOGEN Research Institute, Str. Pasteur, f.n., Cluj-Napoca 400006, Romania

as imperfect ligands to nuclear hormone receptors, non-nuclear cell membrane receptors, or allosteric sites, and leading to agonistic, antagonistic, or even unexpected effects at very low concentrations [4, 5]. However, impacts on human health have remained controversial, given the small potency relative to endogenous hormones and dietary phytoestrogens [6–8]. Such properties, in particular, with respect to estrogen [9], have galvanized concern among investigators and clinicians alike, in terms of a potential impact for environmental pollutants on female infertility.

Using the clinical definition of no pregnancy within 12 months of regular, unprotected, heterosexual intercourse [10, 11], approximately 9 % (72.4 million) of women worldwide suffer from infertility [12], 15 % of women in the U.S. [13•]. Around 30 % of infertility cases are "unexplained" [14], and this appears to be increasing. Between 1982 and 2002, the number of U.S. women reporting difficulties conceiving and maintaining a pregnancy grew by 60 %, whereas the change exceeded 200 % for women <25 years of age [15]. Delayed childbearing, increasing obesity, changes in cigarette smoking, and shifts in the prevalence of sexually transmitted infections are important determinants of female infertility [16]. However, an important role for environmental pollutants is suspected by researchers and clinicians [17, 18].

"Emerging" Organic Pollutants

Since the mid-twentieth century, the enormous success of the chemical industry has fostered an explosion in the volume and array of synthetic organic compounds to which women are exposed [19–21]. While these developments have dramatically improved lives and augmented modern conveniences and comforts, growing evidence also implicates widely distributed organic agents as risk factors for female infertility [22, 23].

Much epidemiologic attention to date has focused on the impact "legacy" organic pollutants, compounds identified by the Stockholm convention as persistent and toxic, tend to redistribute over large geographic areas via global distillation process, and that bioaccumulate [24]. However, investigators have more recently devoted greater attention to impacts of non-persistent pollutants, that are rapidly metabolized and excreted, yet demonstrate estrogenic activity in vitro or in vivo [25]. Exposure to these "emerging" organic pollutants (EOPs) is widespread and frequent, often via use of consumer and personal care products (PCPs) [26, 27], potentially leading to "pseudo-persistence." In this paper, we focus on phthalate diesters, environmental phenols (bisphenol A (BPA) and triclosan), and ultraviolet (UV) filters, EOPs which have generated the most attention to date as potential risk factors for female infertility.

Phthalate Diesters

These high volume production compounds are variously mixed into plastics to impart flexibility and are used as solvents for cosmetics, PCPs, and fragrances [28]. Phthalates exposure is widespread in the U.S.; seven urine monoesters were detected in >75 % of the 1999–2000 population, with higher levels measured in females [29]. Humans are exposed when phthalate diesters in packaging migrate into food or beverages, shed from surfaces, or volatilize, with subsequent gastrointestinal, dermal, and respiratory absorption [30]. Absorbed phthalate diesters are rapidly hydrolyzed into primary monoester forms and may undergo further oxidative metabolism into secondary forms [31]. The parent diesters and their metabolite monoesters possess various estrogenic and anti-estrogenic activities in vitro with ovarian and uterine toxicity in vivo [28]. In humans, urine phthalates have been associated with endometriosis [32], and higher levels around the time of conception have been associated with pregnancy loss [33].

Environmental Phenols

BPA is a high volume production compound used in the manufacture of polycarbonate plastics, epoxy resin can liners, and heat transfer papers [34]. Estrogenic and anti-estrogenic activities have widely been reported in vitro [35] and in vivo [36], and the experimental literature describes ovarian and uterine toxicity [34]. In humans, higher levels of BPA were associated with poorer ovarian response and lower fertilization rates during in vitro fertilization (IVF) cycles [37–39], polycystic ovary syndrome [40], and pregnancy loss [41]. Still, experimental human data suggests rapid inactivation and excretion of ingested BPA, the primary exposure route [42]. This has led to an ongoing controversy regarding the relevance of background exposures for human health [43, 44]. BPA was detected in 92.6 % of urine specimens collected from the 2003–2004 U.S. population, with higher levels in females [45].

Triclosan is added to myriad consumer goods and PCPs to impart "antibacterial" properties [46]. It is structurally homologous to BPA [47], and experimental evidence in vitro indicates estrogenic, anti-estrogenic, and anti-androgenic activities [48, 49], however not necessarily confirmed in vivo [46]. Still, experimental data reported a higher rate of implantation failures among mice treated with high doses of triclosan [50]. Triclosan was detected in 74.6 % of urine specimens collected from the 2003–2004 U.S. population [51].

Ultraviolet Filters

Benzophenones comprise a family of compounds and their metabolites, used as chemical UV filters in sunscreens and cosmetics. These are absorbed through the human dermis

[52] and metabolize rapidly, having estrogenic, anti-estrogenic, and anti-androgenic properties in vitro and in vivo [53–55]. Experimental studies in fish showed that benzophenone 2 (BP-2) inhibited oocyte development, decreased egg production, and inhibited spawning [56]. Human exposure to benzophenones is widespread, and sunscreen use appears to be a major contributor [57]. Benzophenone 3 (BP-3) was detected in 96.8 % of urine samples collected from the 2003–2004 U.S. population, with higher levels for reproductive age women [58].

Summary

Our aim in this paper was to identify and summarize the contemporary epidemiologic evidence for EOPs as female infertility risk factors, and to offer recommendations to help guide more definitive future investigations. Throughout this paper, we used the terms "fertility" and "fecundity" synonymously, as the ability to conceive a recognized pregnancy, and infertility as the inability to conceive a recognized pregnancy within 12 months of regular, unprotected, heterosexual intercourse [10, 11].

Literature Search and Evaluation Strategy

We used PubMed and Google Scholar to search the English language literature published during the past 10 years ending October 31, 2015. Using a combination of keywords and manual reference list searches, we captured epidemiologic studies exploring associations between EOPs and female infertility. We retained nine papers for review, describing results from eight epidemiologic studies. As most retained papers addressed several EOPs, we reviewed each study and assigned a relative weight to the results based on a qualitative assessment of study design, study population and size, outcome and exposure assessment strategies, and the data analysis.

- We considered prospective cohort studies with preconception enrollment as an ideal, although admittedly highly resource-intensive design. This approach ensures that exposures preceded outcomes (temporality) [59], and allows for capture of often unrecognized preclinical losses [60]. Prospective approaches also preclude bias from retrospective evaluation of clinically pregnant women, which exclude by design, those with preclinical loss and infertility [61]. Still, couples planning a pregnancy tend to be less fertile on average than all pregnancies including highly fertile contraception failures, which account for almost half of all U.S. pregnancies [62]. This might introduce a selection bias towards the null hypothesis, if failures have substantially lower exposure, or away from the null if exposure is substantially higher among failures [60].
- We considered general population samples as ideal, with larger sizes likely to have greater sensitivity (statistical power) and to provide more precise effect estimates. Populations using assisted reproductive technologies (ART), including IVF, tend to be "highly selected," comprised of couples who intensely desire but are unable to have a child, seek medical attention for infertility, and have exhausted conventional treatments [63, 64]. If social and economic factors governing ART usage, such as higher income, are also associated with exposure to EOPs, generalizability may be limited [63, 65]. For example, greater wealth was associated with higher urine BP-3 levels and lower urine MBP and MiBP levels in U.S. biomonitoring studies [66]. Still, general population recruitment poses significant challenges, given that <1–2 % of reproductive aged couples reported to be planning near future pregnancies [67–69], and high participant study burdens appear to be better tolerated by reproductive health clinic populations [65].
- We considered prospective capture of time to pregnancy (TTP), the number of menstrual cycles with unprotected heterosexual intercourse prior to a pregnancy, coupled to hCG testing on the day of expected menses, as ideal for outcome assessment. TTP is "functional" in that it integrates various couple-level biological and behavioral processes necessary for pregnancy [60]. Although retrospective self-report appears valid [70], moderate-level misclassification is likely in particular for women with longer waiting times [71]. Use of hCG urine biomarkers of implantation on the day of expected menses also allows for capture of otherwise unobserved preclinical losses [72]. We also considered repeated collection of valid exposure biomarkers as ideal [73]. EOPs have short ½-lives in vivo, and exposure may be episodic, leading to high within-woman variability and lower statistical power [74]. Prospective collection of biologic specimens timed to critical biologic windows for pregnancy was similarly of importance [75].
- Infertility data are frequently hierarchical in nature, and so, use of appropriate statistical techniques to accommodate correlated outcomes was essential [76]. Outcomes from individual menstrual cycles or ART/IVF cycles are correlated within woman, violating the independent outcomes assumption underpinning conventional statistical tests. Investigators frequently employed Cox-discrete time regression to assess relations between EOPs and TTP [77]. Exponentiation of the regression coefficients provide fecundability (fertility) odds ratios (FORs), interpreted as a lower odds for pregnancy with an increase in the predictor if FOR < 1.0 (lower fertility) and a higher odds for pregnancy if FOR > 1.0 (higher fertility). We

likewise assessed appropriate statistical adjustment for confounders, additional infertility risk factors also associated with exposure to EOPs, yet not falling within the causal pathway, such as age, race, body mass index (BMI), and cigarette smoking, inattention to which biases results [78].

Results and Discussion

We identified seven studies that assessed female infertility and phthalates [79••, 80, 81••, 82••, 83–85], five for BPA [79••, 80, 81••, 82••, 86••], and one study each for triclosan [79••] and UV filters [87••]. Table 1 provides an overview of all studies, including detailed lists of exposures and confounders.

Longitudinal Investigation of Fertility and the Environment Study

This prospective investigation with preconception enrollment recruited 501 couples from Michigan and Texas, during 2001–2009. Of eligible couples, 42 % agreed to participate; most were white and had high incomes [81••, 87••]. Couples were followed from the time they stopped using contraception until either a pregnancy or 12 months of trying, completed study questionnaires and daily journals, and provided biologic specimens. Women were provided with fertility monitors to help time intercourse to ovulation and with digital pregnancy detection devices for use on the day of expected menses.

Longitudinal investigation of fertility and the environment (LIFE) investigators measured 14 phthalate monoesters, BPA, and five benzophenones in baseline urine specimens. Associations were evaluated for each phthalate, BPA, and benzophenone on TTP censored at 12 months in 424 couples, adjusted for male exposure and confounders, and accounting for left truncation due to pre-study time off of contraception [81••, 87••]. One standard deviation higher concentrations of mono (2-ethyl-5-carboxypentyl) phthalate (MECPP) (FOR = 1.22; 95 % CI = 1.02–1.47; $P < 0.05$) and mono-n-octyl phthalate (MOP) (FOR = 1.18; 95 % CI = 1.03–1.35; $P < 0.05$) were associated with shorter TTP, although MOP was mostly below the limit of detection (LOD). No other statistically significant female effects were reported. However, significant FORs <1.00 were reported for male exposure to mono-methyl phthalate (MMP), monobenzyl phthalate (MBzP), and BP-2. LIFE Study EOPs were generally lower than those reported for U.S. women of reproductive age in 2001–2009 [88].

Overall, we afforded high weight to the LIFE Study results. Although of moderate sample size, a general population sample was enrolled preconception, and male partner data was concurrently modeled with females in a comprehensive analysis incorporating confounding variables. However, the use of a single baseline urine may have misclassified exposure at conception, leading to underestimated effects, in particular for phthalates and BPA [89, 90].

North Carolina Early Pregnancy Study

This prospective investigation with preconception enrollment recruited 221 women planning pregnancies from North Carolina, in 1982–1986 [82••]. Women were followed from the time they stopped using contraception until either a pregnancy or six months of trying, completed study questionnaires and daily diaries, and collected first morning urine voids. The investigators analyzed a panel of 11 common phthalate monoesters and BPA in pooled residual weekly urine specimens from each menstrual cycle. Confounder-adjusted associations were evaluated for cycle-specific phthalates and BPA with TTP censored at six months, as determined by urine hCG testing. There were no statistically significant associations for phthalates or BPA and fertility. In fact, higher concentrations of several phthalates were associated with a lower odds for preclinical pregnancy loss. Still, in an unadjusted analysis of $n = 94$ contributing both non-conception and conception cycles, the odds for pregnancy was lower with higher monobutyl phthalate (MBP) (odds ratio $[OR]_{3rd\ vs.\ 1st\ tertile} = 0.3$; 95 % CI 0.1–0.8; $P = 0.01$) and the sum of diethyl hexyl phthalate (DEHP) metabolites ($OR_{3rd\ vs.\ 1st\ tertile} = 0.4$; 95 % CI 0.2–1.0; $P = 0.04$). However, this paired analysis excluded the most and the least fertile women, as defined by those who conceived in the first study cycle and those who did not conceive during follow-up, respectively. North Carolina Early Pregnancy Study (NCEPS) EOPs were generally higher than those reported for U.S. women of reproductive age in 2009–2010.

Overall, we afforded high weight to the NCEPS results. Women were enrolled preconception, and urine biomarkers were employed to ascertain pregnancy and exposures. This was also the first study to leverage cycle-specific exposures in a general population sample, and multiple specimens were pooled to reduce exposure variability within-cycle. However, the study results were limited by the absence of male partner data and a modest sample size. Still, data were appropriately analyzed, confounding addressed, and appropriate sensitivity analyses conducted.

Maternal-Infant Research on Environmental Chemicals Study

This retrospective investigation enrolled 2001 pregnant women prior to 14-week completed gestation, residing in ten Canadian cities, from 2008–2011 [79••]. Of eligible women, 39 % agreed to participate and tended to be wealthier and more educated than the general population. Participants

Table 1 Summary of reviewed epidemiologic studies of emerging organic pollutants and female infertility

Citation	*n*	Temporality	Population	Outcome	Exposure	Adjusted?	Primary results
Buck Louis et al., 2014 [81]***	424	Prospective	Preconception	TTP	Urine MCPP	Yes[a]	FOR = 1.22; 95 % CI 1.02–1.47
""	""	""	""	""	Urine MOP	""	FOR = 1.18; 95 % CI 1.03–1.35
""	""	""	""	""	12 urine phthalates[b]	""	FOR = 0.95–1.08; $P > 0.05$
""	""	""	""	""	Urine BPA	""	FOR = 0.96; 95 % CI 0.83–1.10
Buck Louis et al., 2014 [87]***	424	Prospective	Preconception	TTP	Five urine benzophenones[c]	Yes[d]	FOR = 0.79–1.20; $P > 0.05$
Jukic et al., 2015 [82]***	221	Prospective	Preconception	TTP	11 urine phthalates[e]	Yes[f]	No association; $P > 0.05$
""	""	""	""	""	Urine BPA	""	No association; $P > 0.05$
Velez et al., 2015 [79]**	1491	Retrospective	Pregnant	TTP	11 urine phthalates[g]	Yes[h]	FOR = 1.00–1.08; $P > 0.05$
""	1623	""	""	""	Urine BPA	""	FOR = 1.0; 95 % CI 0.92–1.07
""	1583	""	""	""	Urine triclosan	""	FOR = 0.94; 95 % CI 0.88–1.01 [i]
Specht et al., 2015 [85]**	938	Retrospective	Pregnant	TTP	Serum proxy-MEHP[j]	Yes [k]	FOR = 1.14; 95 % CI 1.00–1.30
""	""	""	""	""	Serum proxy-MiNP[l]	""	FOR = 0.98; 95 % CI 0.90–1.06
""	""	""	""	TTP > 13 months	Serum proxy-MEHP[j]	""	OR = 0.86; 95 % CI 0.64–1.14
""	""	""	""	""	Serum proxy-MiNP[l]	""	OR = 1.09; 95 % CI 0.90–1.31
Burdorf et al., 2011 [84]**	3,719	Retrospective	Pregnant	TTP > 6 months	Workplace phthalates	Yes[m]	OR = 2.16; 95 % CI 1.02–4.57
Mínguez-Alarcón et al., 2015 [86••]***	256	Prospective	IVF patients	Implantation	Urine BPA	Yes[n]	*P* trend for quartiles = 0.58
""	""	""	""	Pregnancy	""	""	*P* trend for quartiles = 0.47
""	""	""	""	Live birth	""	""	*P* trend for quartiles = 0.79
Caserta et al., 2013 [80]*	61	Cross-sectional	Clinic and pregnancy	Infertility diagnosis	Serum MEHP, DEHP, BPA > LODs	No	Differences = 3.7 %, 0 % ($P > 0.05$), and 49.8 % ($P < 0.05$)

Table 1 (continued)

Citation	*n*	Temporality	Population	Outcome	Exposure	Adjusted?	Primary results
Tranfo et al., 2012 [83]*	112	Cross-sectional	Clinic and prior birth	Infertility diagnosis	Urine MBP	No[o]	Median case > control; $P < 0.001$
""	""	""	""	""	Urine MEHP + MEHHP	""	Median case > control; $P = 0.076$
""	""	""	""	""	Urine MBzP	""	Median case > control; $P = 0.071$
""	""	""	""	""	Urine MEP	""	Median case > control; $P < 0.001$

BMI body mass index, *BPA* bisphenol A, *BP-1* benzophenone-1, *BP-2* benzophenone-2, *BP-3* benzophenone-3, *BP-8* benzophenone-8, *DEHP* diethyl hexyl phthalate, *FOR* fecundability (fertility) odds ratio, *IVF* in vitro fertilization, *LODs* limits of detection, *MBP*, mono-n-butyl phthalate, *MBzP* monobenzyl phthalate, *MCHP* monocyclohexyl phthalate, *MCMHP* mono-[2-(carboxymethyl)hexyl] phthalate, *MCNP* monocarboxynonyl phthalate, *MCOP* monocarboxyoctyl phthalate, *MCPP* mono(3-carboxypropyl) phthalate, *MECPP* mono-(2-ethyl-5-carboxypentyl) phthalate, *MEHHP* mono-(2-ethyl-5-hydroxyhexyl) phthalate, *MEHP* mono-2-ethylhexyl phthalate, *MEOHP* mono-(2-ethyl-5-oxohexyl) phthalate, *MEP* monoethyl phthalate, *MiBP* mono-isobutyl phthalate, *MiNP* mono-isononyl phthalate, *MMP* monomethyl phthalate, *MOP* mono-n-octyl phthalate, *OR* odds ratio, *4-OH BP* 4-hydroxybenzophenone, *7cx-MMeOP* mono-4-methyl-7-carboxyheptyl phthalate, *7OH-MMeOP* mono-4-methyl-7-hydroxy-octyl phthalate, *7oxo-MMeOP* mono-4-methyl-7-oxo-octyl phthalate, *TTP* time to pregnancy

*** Study results afforded high, ** moderate, or * modest weight, after review

[a] Male partner's exposure, couple's urine creatinine and BMI, woman's age, the difference between partners' ages, female serum cotinine, and study site

[b] Including MBP, MBzP, MCHP, MCMHP, MECPP, MEHHP, MEHP, MEOHP, MEP, MiBP, MiNP, and MMP

[c] Including BP-1, BP-2, BP-3, BP-8, and 4-OH BP

[d] Male partner's exposure, couple's urine creatinine and BMI, woman's age, the difference between partners' ages, female serum cotinine, study site, and season of enrollment

[e] Including MiBP, MBP, MBzP, MCNP, MCOP, MCPP, MECPP, MEHHP, MEHP, MEOHP, and MEP

[f] Urine creatinine, age, age at menarche, smoking, alcohol intake over time, BMI, caffeine consumption over time, and education

[g] Including MBP, MBzP, MCHP, MCPP, MEHHP, MEHP, MEOHP, MEP, MiNP, MMP, and MOP

[h] Urine specific gravity, maternal age, maternal smoking, education, income, and BMI

[i] FOR = 0.84 (95 % CI 0.72–0.97) for triclosan >75th %tile

[j] Including MEHHP, MECPP, and MEOHP

[k] Age, BMI, smoking in pregnancy, frequency of intercourse, parity status, and gestational week at interview

[l] Including 7cx-MMeOP, 7OH-MMeOP, and 7oxo-MMeOP

[m] Age, education, country of origin, parity, smoking and alcohol use in mid-pregnancy, paid employment, and workplace exposures to lifting, pesticides, and solvents

[n] Urine specific gravity, age, BMI, smoking, race, and infertility diagnosis

[o] Phthalates normalized to urine creatinine

completed questionnaires and provided biologic specimens. The investigators analyzed 11 phthalate monoesters, BPA, and triclosan in the first trimester urine specimens. Associations were evaluated for urine phthalates ($n = 1491$), BPA ($n = 1623$), and triclosan ($n = 1583$) with TTP, adjusted for confounders. Urine triclosan >75th percentile was associated with longer TTP (FOR = 0.84; 95 % CI 0.72–0.97; $P < 0.05$), although not statistically significant when expressed as standard deviations or quartiles. No other statistically significant effects were reported. Results were similar when including pregnancies resulting from contraception failures, to accommodate potential selection bias associated with higher fertility in this group. Maternal-infant research on environmental chemicals (MIREC) triclosan was lower than reported for prior studies of pregnant women, BPA was lower than that reported for Canadian females in 2007–2009, and phthalates levels were similar to those in Canadian women in 2009–2011.

Overall, we afforded moderate weight to the MIREC Study results. Women with pregnancies were recruited, and TTP was assessed retrospectively without incorporation of male factors. Furthermore, misclassification associated with the use of a first trimester urine biomarker for retrospective exposure assignment is likely to underestimate effects, in particular for phthalates and BPA [89, 90]. However, the large study size provided for ample statistical power to detect modest associations, and comprehensive statistical and sensitivity analyses were completed.

INUENDO Study

This retrospective investigation recruited 1710 pregnant women and male partners from Warsaw (Poland), Kharkiv (Ukraine), and across Greenland [85], in 2002–2004. Overall, 44.6 % of eligible women enrolled, tending to be somewhat older than non-enrollees, although this varied by site. Participants completed a study questionnaire and provided a blood specimen, in which three secondary phthalate monoesters of DEHP and diisononyl phthalate (DiNP) were determined, the concentrations of which varied by site. Sums of DEHP metabolites ("proxy-MEHP") and DiNP metabolites ("proxy-MiNP," mono-isononyl phthalate) were assessed as predictors of TTP censored at 13 months, and as predictors of TTP >13 months, adjusted for confounders, in 938 women. Log unit increases in proxy-MEHP were associated with shorter TTP in the overall sample (FOR = 1.14; 95 % CI 1.00–1.30; $P < 0.05$), driven primarily by the Greenland subsample. No statistically significant associations were reported for proxy-MiNP or for TTP >13 months. Similar results were reported using tertiles of exposure and restricted to first time pregnancies, although a log unit increase in proxy-MiNP diminished fecundity in primiparous women from Greenland (FOR = 0.72; 95 % CI 0.54–0.95; $P < 0.05$). Men from Greenland had shorter TTP with higher proxy-MEHP and proxy-MiNP, and for proxy-MiNP in all men.

Overall, we afforded moderate weight to the results of the INUENDO Study. Despite retrospective capture of TTP in a pregnant cohort, coupled to a single measure of phthalates exposure, primarily in mid to late pregnancy, the study sample was large overall. Serum specimens were used to measure phthalate exposure, yet the analysis was limited to secondary, oxidative metabolites, and so, the results are unlikely to be vulnerable to criticism levied against determination of primary, hydrolytic phthalate monoesters and BPA in bioactive media including blood [91]. Unfortunately, the results for individual phthalates as predictors were not provided (although reported to be similar), complicating interpretation of the proxy-DEHP and proxy-DiNP effects. Furthermore, female models were not adjusted for males, although exposure was captured. Still, the data were comprehensively analyzed and confounding addressed. However, there exists debate with respect to adjustment for parity in studies of non-persistent exposures [92]. Similar results were generated for $n = 552$ primiparae, but results restricted to multiparous women were not reported.

Generation R Study

This retrospective investigation recruited 8880 pregnant women residing in Rotterdam (Netherlands) and with delivery dates from 2002–2006 [84]. Overall 61 % of eligible women enrolled, tending to be older, more educated, and non-minority relative to non-enrollees. Workplace phthalates exposure was assessed as a predictor of TTP >6 months, adjusted for confounders and additional workplace risks, in 3719 women. Using a job-exposure-matrix (JEM), women with phthalates exposure had higher odds for TTP >6 months than women without exposure (OR = 2.16; 95 % CI 1.02–4.57; $P < 0.05$), similar to the unadjusted effect (OR = 2.70; 95 % CI 1.31–5.55; $P < 0.05$), and when limited to only primiparous women (OR = 1.84). Statistically significant effects were not detected using self-reported workplace exposures.

Overall, we afforded moderate weight to the results of the Generation R Study. Despite retrospective capture and dichotomization of TTP at mid-pregnancy, this was a population-based study with a large sample. Exposure was assessed indirectly using questionnaire data, but also integrated into a JEM to reduce misclassification. However, JEM assignment was based solely on job title, and a validation analysis reported poor agreement with urine exposure biomarkers [93]. Yet, exposure misclassification would be likely to have attenuated effect estimates. Still, the data were comprehensively analyzed and confounding addressed.

Environment and Reproductive Health Study

This prospective investigation of couples using assisted reproductive technologies to conceive began in 2004 at a Massachusetts reproductive health center and is ongoing

[86••]. Approximately 60 % of eligible women agreed to enroll. The most recent Environment and Reproductive Health (EARTH) analysis considered 256 women who completed ≥1 non-donor, fresh embryo transfer, and IVF cycle from 2004–2012. Participants completed study questionnaires, and most provided two urine specimens per cycle, in which BPA was determined. Associations were assessed between cycle-specific BPA and embryo implantation, assessed by serum hCG, clinical pregnancy, assessed by ultrasound, and live birth, adjusted for confounders. Contrary to an early report analyzing $n = 137$ recruited from 2004–2010 [94], no associations were indicated in this larger analysis. Secular changes in IVF success rates and BPA exposures did not account for the discrepancy. The average BPA was similar to that reported for 2009–2012 U.S. females.

Overall, we afforded high weight to the EARTH Study results. Although a clinic study population of moderate size was considered, the prospective nature of the design, and comprehensive specimen collection and follow-up allowed for capture of cycle-specific exposures and a spectrum of outcomes. Exposure misclassification is possible given the short half-life of BPA, yet it was likely modest given that two specimens were averaged for most cycles. Furthermore, an infertile reference group precluded the introduction of selection bias, likely if comparing clinic to non-clinic populations [65]. However, this also may limit generalizability of study results, as women conceiving spontaneously may have different characteristics leading to exposure [63, 64]. In addition, male exposures were not incorporated. However, the data were comprehensively analyzed and confounding addressed. There exists debate with respect to adjustment for infertility diagnosis in studies of clinic populations [95], yet similar results were generated when excluding diagnosis from the models. Discrepancies between the results of the recent [86••] and the 2012 [94] analyses demonstrate the difficulties inherent to this area of research.

Italian Studies

From 2009–2010, the pilot PREVIENI Study enrolled 48 women receiving infertility treatment at a reproductive health center in Rome and 13 residents who had conceived spontaneously within one year [80]. Participants completed a study questionnaire and a fasting blood specimen was collected into glass. Proportions of values >LODs for serum MEHP, DEHP, and BPA were compared between infertile and fertile women. There were no statistically significant differences for MEHP or DEHP, although a higher proportion of infertile women had BPA > LOD (49.8 %; $P < 0.05$). Higher concentrations of estrogen, androgen, and pregnane X receptors measured in peripheral blood monocytes were also reported for infertile vs. fertile women ($P < 0.05$).

A second study conducted in Rome enrolled 56 couples receiving treatment for infertility at a reproductive health center and 56 local couples with a history of childbirth following spontaneous conception [83]. Five phthalate monoesters were determined in spot urine samples, and participants completed a study questionnaire. Higher median levels of creatinine-corrected urine MBP ($P < 0.001$), MEHP + mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) ($P = 0.076$), MBzP ($P = 0.071$), and monoethyl phthalate (MEP) ($P < 0.001$) were reported for infertile vs. fertile women. Significant differences in urine MBP and MEP were also reported for male partners.

Overall, we afforded the results of the two Italian studies modest weight. Although employing biomarkers of exposure, the small sample sizes and cross-sectional nature of the assessments limited the impact of the results. In addition, no adjustments were made for confounders, although PREVIENI reported similar age and BMI in the groups. Importantly, women receiving infertility treatment may be dissimilar to the general population in terms of behavior influencing exposure [63, 64], and medical therapy may itself inflate exposure [30], and so, a clinic-based comparison group is preferable [65]. An additional concern comes from the use of serum biomarkers to determine primary phthalate monoesters and BPA, which was criticized due to a possibility for extraneous introduction of parent compounds into the specimen during collection, with subsequent in situ metabolism by endogenous hydrolases, and so urine preferred [91].

Conclusions

Whereas a substantial experimental literature has begun to accumulate, very few epidemiologic studies considering the impact of EOPs on female infertility have been published to date. We afforded high weight to the results in four of nine identified publications [81••, 82••, 86••, 87••] and moderate weight to three [79••, 84, 85]. Results were almost uniformly null, although study participants tended to be wealthier and more highly educated than the general population, and exposure levels for contemporary samples tended to be lower, potentially limiting extrapolation to poorer, less educated groups. Overall, we conclude that insufficient evidence exists at present to implicate background exposures to phthalates and BPA as risk factors for women's infertility, defined as 12 months of unprotected heterosexual intercourse without a pregnancy [10, 11], although more highly exposed groups may be vulnerable. As only one reviewed study reported results for triclosan and one for UV filters, we are unable to draw conclusions. Still, given the paucity of data and limitations to available evidence, we believe additional investigations are needed to more definitively assess the risks.

Female infertility is a critical human health issue, and apparent increases over recent decades implicate environmental in addition to sociologic factors [17, 18]. Exposure to EOPs is frequent and widespread among women of reproductive age, drawing considerable attention to impacts on women's fertility [1•, 2•, 3]. EOPs are not limited to the phthalates, BPA, and UV filters considered in this paper, but encompass a broader array of compounds to which women are exposed as new and replacement compounds enter the market [96]. However, population data are scant. For example, parabens, used as preservatives and anti-oxidants in PCPs and dietary applications [97], were detected in 99 % of U.S. females in 2005–2006 [98]. Recent human evidence suggests associations between parabens and diminished ovarian reserve [99], yet no epidemiologic studies of female infertility appear to have been published to date.

The evolution of the exposome paradigm [100] has brought greater attention to the relevance of chemical mixtures, contact with which more accurately reflects the human experience than do models of isolated exposures. The "mixing" of female and male exposures reviewed in this paper speak to this issue as well, as suggested by the couple-level exposure results from the LIFE study [81••, 87••]. Additive or synergistic effects may manifest in the absence of individual effects at low doses [101], and impacts may be higher in susceptible groups, due to genetic background, co-existing exposures, and pre-existing conditions [102]. Yet, exposure assessment presents a challenge. The large within-woman variabilities for many EOPs may lead to "false negative" studies when relying on single or "mistimed" biomarker collections [74]. Longitudinal designs with repeated specimen collection to reduce exposure misclassification, comprehensive chemical analyses, and appropriate statistical methods to assess mixtures are desired in both the general population and high-risk groups to more definitively assess impacts. Epidemiologists have only begun to piece together the relevance of EOPs to female infertility. Additional well-planned studies will help to build the critical literature mass necessary for identifying modifiable environmental risk factors, to prevent and to help to treat female infertility.

Acknowledgments The authors would like to extend their gratitude to Oliver Chakirou, PhD, for his generous assistance with the literature search during the early stages of this work.

Compliance with Ethical Standards

Conflict of Interest Michael S. Bloom, Romeo Micu, and Iulia Neamtiu declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin Jr JN, et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. Int J Gynaecol Obstet. 2015;131(3):219–25. **This paper describes international gynecological and obstetrical community concerns that environmental pollutants are risk factors for reproductive health problems. Reproductive health professionals are encouraged to take an active role in reducing exposures on behalf of their patients and in advocating for policy changes**.

2.• American College of Obstetricians and Gynecologists, American Society for Reproductive Medicine. Committee opinion no. 575: exposure to toxic environmental agents. Obstet Gynecol. 2013;122(4):931–5. **This paper and an accompanying literature review formally recognize environmental pollutants as risk factors for adverse reproductive health outcomes and infertility, on behalf of the U.S. gynecologic, obstetrics, and reproductive endocrinology communities. Clinicians are advised to actively advocate for U.S. policy changes to reduce exposures among women and to recognize the role of environmental pollutants when treating patients**.

3. Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society. Endocrinology. 2012;153(9):4097–110.

4. Kiyama R, Wada-Kiyama Y. Estrogenic endocrine disruptors: molecular mechanisms of action. Environ Int. 2015;83:11–40.

5. Colborn T, Vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environ Health Perspect. 1993;101(5):378–84.

6. Zoeller R, Bergman A, Becher G, Bjerregaard P, Bornman R, Brandt I, et al. A path forward in the debate over health impacts of endocrine disrupting chemicals. Environ Heal. 2014;13(1):118.

7. Nohynek GJ, Borgert CJ, Dietrich D, Rozman KK. Endocrine disruption: fact or urban legend? Toxicol Lett. 2013;223(3):295–305.

8. Foster WG, Neal MS, Han MS, Dominguez MM. Environmental contaminants and human infertility: hypothesis or cause for concern? J Environ Sci Heal B Crit Rev. 2008;11(3–4):162–76.

9. Yoon K, Kwack SJ, Kim HS, Lee B-M. Estrogenic endocrine-disrupting chemicals: molecular mechanisms of actions on putative human diseases. J Toxicol Environ Health B Crit Rev. 2014;17(3):127–74.

10. American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss: a committee opinion. Fertil Steril. 2013;99(1):63.

11. Larsen U. Research on infertility: which definition should we use? Fertil Steril. 2005;83(4):846–52.

12. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod. 2007;22(6):1506–12.

13.• Thoma ME, McLain AC, Louis JF, King RB, Trumble AC, Sundaram R, et al. Prevalence of infertility in the United States as estimated by the current duration approach and a traditional constructed approach. Fertil Steril. 2013;99(5):1324–31.e1. **This paper describes use of a 'current duration approach' for**

estimating U.S. infertility, incorporating only women at risk for pregnancy in the denominator, in contrast to the 'traditional constructed approach,' incorporating all married reproductive age women in the denominator. The results contradict earlier reports of declining infertility among U.S. women.

14. Kashir J, Heindryckx B, Jones C, de Sutter P, Parrington J, Coward K. Oocyte activation, phospholipase C zeta and human infertility. Hum Reprod Update. 2010;16(6):690–703.
15. Woodruff TJ, Schwartz J, Giudice LC. Research agenda for environmental reproductive health in the 21st century. J Epidemiol Community Health. 2010;64(4):307–10.
16. Baird DT, Collins J, Egozcue J, Evers LH, Gianaroli L, Leridon H, et al. Fertility and ageing. Hum Reprod Update. 2005;11(3):261–76.
17. Macaluso M, Wright-Schnapp TJ, Chandra A, Johnson R, Satterwhite CL, Pulver A, et al. A public health focus on infertility prevention, detection, and management. Fertil Steril. 2010;93(1), 16.e1-.e0.
18. Petraglia F, Serour GI, Chapron C. The changing prevalence of infertility. Int J Gynaecol Obstet. 2013;123:S4–8.
19. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ Health Perspect. 2011;119(6):878–85.
20. Thompson RC, Swan SH, Moore CJ, vom Saal FS. Our plastic age. Philos Trans R Soc Lond B Biol Sci. 2009;364(1526):1973–6.
21. Organization of Economic Cooperation and Development (OECD). 40 years of chemical safety at the OECD: quality and efficiency. Paris, France 2011.
22. Sutton P, Woodruff TJ, Perron J, Stotland N, Conry JA, Miller MD, et al. Toxic environmental chemicals: the role of reproductive health professionals in preventing harmful exposures. Am J Obstet Gynecol. 2012;207(3):164–73.
23. Yang CZ, Yaniger SI, Jordan VC, Klein DJ, Bittner GD. Most plastic products release estrogenic chemicals: a potential health problem that can be solved. Environ Health Perspect. 2011;119(7):989–96.
24. Secretariat of the Stockholm Convention. Stockholm Convention: overview. Châtelaine, Switzerland: United Nations Environment Programme (UNEP); 2008. Available from: http://chm.pops.int/TheConvention/Overview/tabid/3351/Default.aspx.
25. Buck Louis GM, Bloom MS, Gatto NM, Hogue CR, Westreich DJ, Zhang C. Epidemiology's continuing contribution to public health: the power of "then and now". Am J Epidemiol. 2015;181(8):e1–8.
26. Calafat AM, Valentin-Blasini L, Ye X. Trends in exposure to chemicals in personal care and consumer products. Curr Envir Health Rpt. 2015;2(4):348–55.
27. CDC. Fourth national report on human exposure to environmental chemicals—updated tables, February 2015. Report. Atlanta: U.S. Centers for Disease Control and Prevention; 2015.
28. Kay VR, Chambers C, Foster WG. Reproductive and developmental effects of phthalate diesters in females. Crit Rev Toxicol. 2013;43(3):200–19.
29. Silva MJ, Barr DB, Reidy JA, Malek NA, Hodge CC, Caudill SP, et al. Urinary levels of seven phthalate metabolites in the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. Environ Health Perspect. 2004;112(3):331–8.
30. Meeker JD, Sathyanarayana S, Swan SH. Phthalates and other additives in plastics: human exposure and associated health outcomes. Philos Trans R Soc Lond B Biol Sci. 2009;364(1526):2097–113.
31. Hauser R, Calafat AM. Phthalates and human health. Occup Environ Med. 2005;62(11):806–18.
32. Upson K, Sathyanarayana S, De Roos AJ, Thompson ML, Scholes D, Dills R, et al. Phthalates and risk of endometriosis. Environ Res. 2013;126:91–7.
33. Toft G, Jönsson BAG, Lindh CH, Jensen TK, Hjollund NH, Vested A, et al. Association between pregnancy loss and urinary phthalate levels around the time of conception. Environ Health Perspect. 2012;120(3):458–63.
34. Peretz J, Vrooman L, Ricke WA, Hunt PA, Ehrlich S, Hauser R, et al. Bisphenol A and reproductive health: update of experimental and human evidence, 2007–2013. Environ Health Perspect. 2014;122(8):775–86.
35. Wetherill YB, Akingbemi BT, Kanno J, McLachlan JA, Nadal A, Sonnenschein C, et al. In vitro molecular mechanisms of bisphenol A action. Reprod Toxicol. 2007;24(2):178–98.
36. Richter CA, Birnbaum LS, Farabollini F, Newbold RR, Rubin BS, Talsness CE, et al. In vivo effects of bisphenol A in laboratory rodent studies. Reprod Toxicol. 2007;24(2):199–224.
37. Bloom MS, Kim D, vom Saal FS, Taylor JA, Cheng G, Lamb JD, et al. Bisphenol A exposure reduces the estradiol response to gonadotropin stimulation during in vitro fertilization. Fertil Steril. 2011;96(3):672–U199.
38. Souter I, Smith KW, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, et al. The association of bisphenol-A urinary concentrations with antral follicle counts and other measures of ovarian reserve in women undergoing infertility treatments. Reprod Toxicol. 2013;42:224–31.
39. Fujimoto VY, Kim D, Vom Saal FS, Lamb JD, Taylor JA, Bloom MS. Serum unconjugated bisphenol A concentrations in women may adversely influence oocyte quality during in vitro fertilization. Fertil Steril. 2011;95(5):1816–9.
40. Kandaraki E, Chatzigeorgiou A, Livadas S, Palioura E, Economou F, Koutsilieris M, et al. Endocrine disruptors and polycystic ovary syndrome (PCOS): elevated serum levels of bisphenol A in women with PCOS. J Clin Endocrinol Metab. 2011;96(3):E480–4.
41. Lathi RB, Liebert CA, Brookfield KF, Taylor JA, vom Saal FS, Fujimoto VY, et al. Conjugated bisphenol A in maternal serum in relation to miscarriage risk. Fertil Steril. 2014;102(1):123–8.
42. Thayer KA, Doerge DR, Hunt D, Schurman SH, Twaddle NC, Churchwell MI, et al. Pharmacokinetics of bisphenol A in humans following a single oral administration. Environ Int. 2015;83:107–15.
43. Vandenberg LN, Hunt PA, Myers JP, Vom Saal FS. Human exposures to bisphenol A: mismatches between data and assumptions. Rev Environ Health. 2013;28(1):37–58.
44. Teeguarden J, Hanson-Drury S, Fisher JW, Doerge DR. Are typical human serum BPA concentrations measurable and sufficient to be estrogenic in the general population? Food Chem Toxicol. 2013;62:949–63.
45. Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Ekong J, Needham LL. Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. Environ Health Perspect. 2005;113(4):391–5.
46. Witorsch RJ. Critical analysis of endocrine disruptive activity of triclosan and its relevance to human exposure through the use of personal care products. Crit Rev Toxicol. 2014;44(6):535–55.
47. Dann AB, Hontela A. Triclosan: environmental exposure, toxicity and mechanisms of action. J Appl Toxicol. 2011;31(4):285–311.
48. Huang HY, Du GZ, Zhang W, Hu JL, Wu D, Song L, et al. The in vitro estrogenic activities of triclosan and triclocarban. J Appl Toxicol. 2014;34(9):1060–7.
49. Gee RH, Charles A, Taylor N, Darbre PD. Oestrogenic and androgenic activity of triclosan in breast cancer cells. J Appl Toxicol. 2008;28(1):78–91.
50. Crawford BR, de Catanzaro D. Disruption of blastocyst implantation by triclosan in mice: impacts of repeated and acute doses and

combination with bisphenol-A. Reprod Toxicol. 2012;34(4):607–13.
51. Calafat AM, Ye X, Wong L-Y, Reidy JA, Needham LL. Urinary concentrations of triclosan in the US population: 2003–2004. Environ Health Perspect. 2008;116(3):303–7.
52. Jiang R, Roberts MS, Collins DM, Benson HAE. Absorption of sunscreens across human skin: an evaluation of commercial products for children and adults. Br J Clin Pharmacol. 1999;48(4):635–7.
53. Molina-Molina J-M, Escande A, Pillon A, Gomez E, Pakdel F, Cavailles V, et al. Profiling of benzophenone derivatives using fish and human estrogen receptor-specific in vitro bioassays. Toxicol Appl Pharmacol. 2008;232(3):384–95.
54. Fent K, Kunz PY, Gomez E. UV filters in the aquatic environment induce hormonal effects and affect fertility and reproduction in fish. Chimia. 2008;62(5):368–75.
55. Krause M, Klit A, Blomberg Jensen M, Søeborg T, Frederiksen H, Schlumpf M, et al. Sunscreens: are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. Int J Androl. 2012;35(3):424–36.
56. Weisbrod CJ, Kunz PY, Zenker AK, Fent K. Effects of the UV filter benzophenone-2 on reproduction in fish. Toxicol Appl Pharmacol. 2007;225(3):255–66.
57. Zamoiski RD, Cahoon EK, Freedman DM, Linet MS. Self-reported sunscreen use and urinary benzophenone-3 concentrations in the United States: NHANES 2003–2006 and 2009–2012. Environ Res. 2015;142:563–7.
58. Calafat AM, Wong L-Y, Ye X, Reidy JA, Needham LL. Concentrations of the sunscreen agent benzophenone-3 in residents of the United States: National Health and Nutrition Examination Survey 2003–2004. Environ Health Perspect. 2008;116(7):893–7.
59. Hill AB. The environment and disease: association or causation? Proc R Soc Med. 1965;58(5):295–300.
60. Baird DD, Wilcox AJ, Weinberg CR. Use of time to pregnancy to study environmental exposures. Am J Epidemiol. 1986;124(3):470–80.
61. Olsen J. Design options and sources of bias in time-to-pregnancy studies. Scand J Work Environ Health. 1999;25:5–7.
62. Finer LB, Zolna MR. Unintended pregnancy in the United States: incidence and disparities, 2006. Contraception. 2011;84(5):478–85.
63. Collins J, Evers H, Golombok S, Hannaford P, Jacobs HS, La Vecchia C, et al. Social determinants of human reproduction. Hum Reprod. 2001;16(7):1518–26.
64. Olsen J, Chinnow M, Spinelli A. Seeking medical help for subfecundity: a study based upon surveys in five European countries. Fertil Steril. 1996;66(1):95.
65. Olsen J, Bonde JP, Hjollund NH, Basso O, Ernst E. Using infertile patients in epidemiologic studies on subfecundity and embryonal loss. Hum Reprod Update. 2005;11(6):607–11.
66. Tyrrell J, Melzer D, Henley W, Galloway TS, Osborne NJ. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001–2010. Environ Int. 2013;59:328–35.
67. Bonde JPE, Hjollund NHI, Jensen TK, Ernst E, Kolstad H, Henriksen TB, et al. A follow-up study of environmental and biologic determinants of fertility among 430 Danish first-pregnancy planners: design and methods. Reprod Toxicol. 1998;12(1):19–27.
68. Buck Louis GM, Schisterman EF, Sweeney AM, Wilcosky TC, Gore-Langton RE, Lynch CD, et al. Designing prospective cohort studies for assessing reproductive and developmental toxicity during sensitive windows of human reproduction and development—the LIFE Study. Paediatr Perinat Epidemiol. 2011;25(5):413–24.
69. Slama R, Ducot B, Carstensen L, Lorente C, De La Rochebrochard E, Leridon H, et al. Feasibility of the current-duration approach to studying human fecundity. Epidemiology. 2006;17(4):440–9.
70. Joffe M, Villard L, Li Z, Plowman R, Vessey M. A time to pregnancy questionnaire designed for long term recall: validity in Oxford. J Epidemiol Community Health. 1995;49(3):314–9.
71. Cooney MA, Buck Louis GM, Sundaram R, McGuiness BM, Lynch CD. Validity of self-reported time to pregnancy. Epidemiology. 2009;20(1):56–9.
72. Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD, Schlatterer JP, Canfield RE, et al. Incidence of early loss of pregnancy. N Engl J Med. 1988;319(4):189–94.
73. Taioli E, Kinney P, Zhitkovich A, Fulton H, Voitkun V, Cosma G, et al. Application of reliability models to studies of biomarker validation. Environ Health Perspect. 1994;102(3):306–9.
74. Lachin JM. The role of measurement reliability in clinical trials. Clin Trials. 2004;1(6):553–66.
75. Buck Louis GM, Yeung E, Sundaram R, Laughon SK, Zhang C. The exposome—exciting opportunities for discoveries in reproductive and perinatal epidemiology. Paediatr Perinat Epidemiol. 2013;27(3):229–36.
76. Buck Louis GB, Dukic V, Heagerty PJ, Louis TA, Lynch CD, Ryan LM, et al. Analysis of repeated pregnancy outcomes. Stat Methods Med Res. 2006;15(2):103–26.
77. Weinberg CR, Baird DD, Rowland AS. Pitfalls inherent in retrospective time-to-event studies—the example of time to pregnancy. Stat Med. 1993;12(9):867–79.
78. Greenland S, Robins J. Identifiability, exchangeability and confounding revisited. Epidemiol Perspect Innov. 2009;6(1):4.
79.•• Velez MP, Arbuckle TE, Fraser WD. Female exposure to phenols and phthalates and time to pregnancy: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. Fertil Steril. 2015;103(4):1011–U210. **This paper is the first to describe an analysis of triclosan exposure and women's fertility, using a retrospective investigation of pregnant women recruited from the general Canadian population. A reduction in fertility was suggested for higher levels of urine triclosan**.
80. Caserta D, Bordi G, Ciardo F, Marci R, La Rocca C, Tait S, et al. The influence of endocrine disruptors in a selected population of infertile women. Gynecol Endocrinol. 2013;29(5):444–7.
81.•• Buck Louis GM, Sundaram R, Sweeney AM, Schisterman EF, Maisog J, Kannan K. Urinary bisphenol A, phthalates, and couple fecundity: the Longitudinal Investigation of Fertility and the Environment (LIFE) Study. Fertil Steril. 2014;101(5):1359–66. **This paper is the first to describe a couple-based longitudinal study of phthalates and BPA in association with women's fertility, in a general population sample. No effects were indicated for preconception urine levels in women, yet reduced fertility was indicated for higher preconception urine phthalates in men**.
82.•• Jukic AM, Calafat AM, McConnaughey DR, Longnecker MP, Hoppin JA, Weinberg CR, et al. Urinary concentrations of phthalate metabolites and bisphenol A and associations with follicular-phase length, luteal-phase length, fecundability, and early pregnancy loss. Environ Health Perspect. 2015. **This paper describes a population-based longitudinal study of urine phthalates and BPA in a 1980s population having experienced higher exposures than contemporary background U.S. levels. Using cycle-specific exposure estimates, no associations were reported for women's fertility**.
83. Tranfo G, Caporossi L, Paci E, Aragona C, Romanzi D, De Carolis C, et al. Urinary phthalate monoesters concentration in couples with infertility problems. Toxicol Lett. 2012;213(1):15–20.
84. Burdorf A, Brand T, Jaddoe VW, Hofman A, Mackenbach JP, Steegers EAP. The effects of work-related maternal risk factors

on time to pregnancy, preterm birth and birth weight: the Generation R Study. Occup Environ Med. 2011;68(3):197–204.
85. Specht IO, Bonde JP, Toft G, Lindh CH, Jonsson BAG, Jorgensen KT. Serum phthalate levels and time to pregnancy in couples from Greenland, Poland and Ukraine. PLoS ONE. 2015;10(3).
86.•• Minguez-Alarcon L, Gaskins AJ, Chiu Y-H, Williams PL, Ehrlich S, Chavarro JE, et al. Urinary bisphenol A concentrations and association with in vitro fertilization outcomes among women from a fertility clinic. Hum Reprod. 2015;30(9):2120–8. **This paper describes a prospective analysis of cycle-specific urine BPA levels in relation to embryo implantation, clinical pregnancy and live birth, in women undergoing IVF. No associations were indicated for BPA and fertility**.
87.•• Buck Louis GM, Kannan K, Sapra KJ, Maisog J, Sundaram R. Urinary concentrations of benzophenone-type ultraviolet radiation filters and couples' fecundity. Am J Epidemiol. 2014;180(12): 1168–75. **This paper is the first to describe an analysis of urine benzophenone UV filters and female fertility, indicating no effect for preconception urine levels in women, but decreased fertility for preconception urine levels in men**.
88. Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville: Department of Health and Human Services, Centers for Disease Control and Prevention (CDC), National Center for Health Statistics; 2005–2010; 2015. Available from: http://www.cdc.gov/nchs/nhanes.htm.
89. Fromme H, Bolte G, Koch HM, Angerer J, Boehmer S, Drexler H, et al. Occurrence and daily variation of phthalate metabolites in the urine of an adult population. Int J Hyg Environ Health. 2007;210(1):21–33.
90. Koch HM, Aylward LL, Hays SM, Smolders R, Moos RK, Cocker J, et al. Inter- and intra-individual variation in urinary biomarker concentrations over a 6-day sampling period. Part 2: personal care product ingredients. Toxicol Lett. 2014;231(2):261–9.
91. Calafat A, Koch H, Swan S, Hauser R, Goldman L, Lanphear B, et al. Misuse of blood serum to assess exposure to bisphenol A and phthalates. Breast Cancer Res. 2013;15(5):403.
92. Howards PP, Schisterman EF, Heagerty PJ. Potential confounding by exposure history and prior outcomes: an example from perinatal epidemiology. Epidemiology. 2007;18(5):544–51.
93. Tielemans E, Heederik D, Burdorf A, Vermeulen R, Veulemans H, Kromhout H, et al. Assessment of occupational exposures in a general population: comparison of different methods. Occup Environ Med. 1999;56(3):145–51.
94. Ehrlich S, Williams PL, Missmer SA, Flaws JA, Berry KF, Calafat AM, et al. Urinary bisphenol A concentrations and implantation failure among women undergoing in vitro fertilization. Environ Health Perspect. 2012;120(7):978–83.
95. Schisterman EF, Cole SR, Platt RW. Over adjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology. 2009;20(4):488–95.
96. Zimmerman JB, Anastas PT. Toward substitution with no regrets. Science. 2015;347(6227):1198–9.
97. Błędzka D, Gromadzińska J, Parabens WW. From environmental studies to human health. Environ Int. 2014;67:27–42.
98. Calafat AM, Ye X, Wong L-Y, Bishop AM, Needham LL. Urinary concentrations of four parabens in the US population: NHANES 2005–2006. Environ Health Perspect. 2010;118(5):679–85.
99. Smith KW, Souter I, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, et al. Urinary paraben concentrations and ovarian aging among women from a fertility center. Environ Health Perspect. 2013;121(11–12):1299–305.
100. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomark Prev. 2005;14(8):1847–50.
101. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Lee DH, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev. 2012;33(3):378–455.
102. Woodruff TJ, Zeise L, Axelrad DA, Guyton KZ, Janssen S, Miller M, et al. Meeting report: moving upstream-evaluating adverse upstream end points for improved risk assessment and decision-making. Environ Health Perspect. 2008;116(11):1568–75.