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Persistent organic pollutants and couple fecundability: a systematic review

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BACKGROUND: Despite increasing regulation, exposure to persistent organic pollutants (POPs) remains a serious public health concern due to their accumulation in the environment and ability to biomagnify up the food chain. POPs are associated with endocrine-disrupting effects including adverse reproductive outcomes that could affect fecundability, i.e. the capacity to conceive a pregnancy, quantified as time to pregnancy (TTP).

OBJECTIVE AND RATIONALE: Results of epidemiologic studies that examine the impact of various chemical classes of POPs on TTP have not been synthesised. We undertook a systematic review to summarise the strength of evidence for associations of four common groups of POPs with couple fecundability and to identify gaps and limitations in the literature in order to inform policy decisions and future research.

SEARCH METHODS: We performed an electronic search of literature published between 1 January 2007 and 6 August 2019 in MEDLINE, EMBASE.com, Global Health, DART/TOXLINE and POPLINE. We included empirical research papers that examined human exposure to organochlorine (OC) pesticides, brominated flame retardants, polychlorinated organic compounds and/or per- and polyfluoroalkyl substances (PFAS) and considered TTP or fecundability as an outcome. Standardised forms for screening, data extraction and study quality were developed using DistillerSR software, and all reviews were completed in duplicate. We used the Newcastle-Ottawa Scale to assess risk of bias and devised additional quality metrics based on specific methodological features of fecundability studies.

OUTCOMES: The search returned 4573 articles, and 28 papers from 19 different studies met inclusion criteria. Among them, four studies measured TTP prospectively, three had data on participants' prenatal exposure, three examined associations in both male and female partners and one focused exclusively on males. Analyses varied widely in terms of exposure characterisation, precluding a meta-analytic approach. Evidence was strongest for adverse associations of female exposure to polychlorinated biphenyls with TTP, with some additional support for associations of female exposure to polybrominated diphenyl ethers and PFAS with longer TTP. Our review provided little or no support for associations between female exposure to OC pesticides or male exposure to any of the POP groups and TTP.

WIDER IMPLICATIONS: Evidence suggests that female exposure to at least some POPs may reduce fecundability. Although many of these chemicals are no longer in production, they are still detectable in human biosamples because of their persistence in the environment. Replacement chemicals that are being introduced as older ones are restricted may have similar reproductive consequences. Future studies should examine these newer POPs, assess interactions between POPs and other chemical and non-chemical exposures, investigate how POPs are distributed in and metabolised by the human body and focus on populations that may be disproportionately exposed.

Key words: time to pregnancy / couple fecundability / systematic review / environmental effects / endocrine-disrupting chemicals / persistent organic pollutants / organochlorine pesticides / brominated flame retardants / polychlorinated biphenyls / perfluoroalkyl substances

Introduction

Persistent organic pollutants (POPs) are stable compounds that were first linked to impaired reproductive function by Rachel Carson, who described breeding failure among birds exposed to dichlorodiphenyltrichloroethane (DDT) in her landmark book, *Silent Spring* (Carson, 1962). Since then, studies have examined associations of various POPs, including organochlorine (OC) pesticides, brominated flame retardants (BFRs), polychlorinated biphenyls (PCBs) and per- and polyfluoroalkyl substances (PFAS), with a range of reproductive outcomes in animals and humans (Gore *et al.*, 2015; Kahn *et al.*, 2020). Ecological data showing a decline in sperm count in industrialised countries coincident with the spread of POP use in the decades following World War II (Carlsen *et al.*, 1992; Swan *et al.*, 2000; Levine *et al.*, 2017) led to the hypothesis that these chemicals may affect male reproductive potential by impairing foetal testicular development (Skakkebaek *et al.*, 2001). Subsequent epidemiologic studies have documented associations of PCBs with reduced semen quality (Meeker and Hauser, 2010), although evidence for associations with other POPs is sparse or conflicting (Vested *et al.*, 2014). It is theorised that environmental chemicals may also alter female reproductive processes, impeding the ability to produce viable oocytes and to establish and maintain a pregnancy (Buck Louis *et al.*, 2011).

Couple fecundity, or the biological ability to reproduce, is a product of both male and female factors. It is most commonly measured as fecundability, or the per-cycle probability of conception when a couple has unprotected intercourse (Baird *et al.*, 1986; Joffe, 1997; Smarr *et al.*, 2017), and is operationalised as time to pregnancy (TTP). Identifying predictors of longer TTP has both clinical and public health relevance. Clinical infertility is defined as TTP >12 months (Zegers-Hochschild *et al.*, 2009) and couples with suspected infertility often seek medical intervention, despite associated personal (Galhardo *et al.*, 2011; Luk and Loke, 2015) and financial costs (Wu *et al.*, 2013) and potential health risks to women and children (Qin *et al.*, 2016). According to 2011–2015 data, 23.6% of currently married, childless women age 15–44 years in the USA have impaired fecundity, i.e. have not successfully carried a pregnancy to term (National Center for Health Statistics, 2020), and the use of assisted reproductive technologies and the number of fertility clinics providing these services continues to increase (Sunderam *et al.*, 2019). While factors such as higher average age at first pregnancy attempt partially explain this increase (Ely and Hamilton, 2018), exposure to endocrine-disrupting chemicals such as POPs may also contribute to the trend.

Because of their stability and predominantly lipophilic properties, POPs persist in soil, air and water as well as in animal tissue, where they can accumulate and biomagnify. Individual POPs may have half-lives from a few weeks to a dozen years or more depending on environmental or physiological conditions. Since the 1970s, a number of POPs have been banned from production, especially in developed countries. OC pesticides were largely restricted in the USA in the 1970s, although they continue to be used in some countries for malaria control (Agency for Toxic Substances and Disease Registry, 2019; Kleanthi *et al.*, 2008). Among the BFRs, polybrominated biphenyls (PBBs) were banned by the USA in 1976 and production of polybrominated diphenyl ethers (PBDEs) was ceased in 2013 (U.S. Environmental Protection Agency, 2017). PCBs were banned in the USA in 1979. PFAS, used to create coatings that resist heat, oil, stains, grease and water, are still widely used, although some are being

regulated and voluntary phase-outs have begun. In 2008, the Stockholm Convention on Persistent Organic Pollutants identified a 'dirty dozen' chemicals that pose severe enough risk to human health to warrant worldwide restriction (United Nations Environment Programme, 2008). Despite the growing environmental and health concerns about POPs, many of these chemicals persist in the food supply, in consumer products and in the built environment. Even those that have been banned are still detectable in most people, albeit at lower concentrations (Wattigney *et al.*, 2015).

Although the biological mechanisms are only partially understood, OC pesticides, BFRs, PCBs and PFAS all exhibit properties that allow them to disrupt endocrine and reproductive processes. The OC pesticide DDT has been shown to bind and activate both alpha and beta oestrogen receptors, and its metabolite, dichlorodiphenyldichloroethylene (DDE), has been shown to be a potent androgen receptor agonist in animal and *in-vitro* studies (Kelce *et al.*, 1995; Klotz *et al.*, 1996; Kuiper *et al.*, 1998). DDT, DDE and dichlorodiphenyldichloroethane, another DDT metabolite, have been associated with testicular (McGlynn *et al.*, 2008), endometrial (Hardell *et al.*, 2004a), breast (Wolff *et al.*, 1993; Safe and Zacharewski, 1997) and pancreatic (Porta *et al.*, 2008) cancers, as well as type 2 diabetes (Codru *et al.*, 2007).

With respect to BFRs, PBDEs have been found to disrupt thyroid hormone homeostasis, perturb expression and oestrogen sensitivity of sex hormone-regulated genes, impair spermatogenesis and alter sexual behaviours in rodents (Kuriyama *et al.*, 2004; Lichtensteiger *et al.*, 2004; Talsness *et al.*, 2007). In humans, certain PBDEs have been associated with decreased semen quality (Abdelouahab *et al.*, 2011; Mumford *et al.*, 2015), altered reproductive hormones in both women (Gao *et al.*, 2016) and men (Meeker *et al.*, 2009; Makey *et al.*, 2016) and poor IVF outcomes (Johnson *et al.*, 2012). Certain PBBs have been linked to prolonged menstrual cycles, extended periods of implantation bleeding, altered testosterone and progesterone metabolism and poor IVF outcomes in animal models (Allen and Lambrecht, 1978; Newton *et al.*, 1982; Kholkute *et al.*, 1994), as well as perturbed menstrual cycle hormones and impaired ovarian function in humans (Davis *et al.*, 2005; Howards *et al.*, 2019).

In-vitro research (Kovacevic *et al.*, 1995; Schrader and Cooke, 2003), animal models (Bergeron *et al.*, 1994; Hany *et al.*, 1999; Kaya *et al.*, 2002) and epidemiological studies (Gore *et al.*, 2015) have all found evidence linking PCBs to endocrine disruption, a plausible conclusion, as certain PCB congeners bear stereochemical resemblance to steroid hormones including oestrogen and testosterone (Connor *et al.*, 1997). In addition to human studies showing cross-sectional associations of higher serum PCB concentrations with lower sperm motility and serum testosterone (Goncharov *et al.*, 2009; Meeker and Hauser, 2010), some evidence suggests that prenatal PCB exposure may result in testicular cancer in males (Hardell *et al.*, 2004b). In women, PCBs have been associated with breast cancer (Recio-Vega *et al.*, 2008; Morgan *et al.*, 2017; Wielsoe *et al.*, 2017) and endometriosis (Cano-Sancho *et al.*, 2019; Wen *et al.*, 2019).

Based on laboratory findings, PFAS could interfere with reproductive function via multiple pathways. In male rodents, PFAS delay Leydig cell maturation, damage seminiferous tubules, increase spermatagonal and Leydig cell apoptosis and decrease testosterone levels. *In-vitro* oocyte studies indicate that PFAS may diminish ovarian reserve and reduce endogenous hormone synthesis by activating peroxisome proliferator-activated receptors, disrupting gap junction intercellular communication between oocyte and granulosa cells, inducing thyroid hormone deficiency, antagonising ovarian enzyme activities involved in ovarian steroidogenesis or inhibiting kisspeptin signalling in the hypothalamus (Ding *et al.*, 2020; Gonsioroski *et al.*, 2020). In humans, perfluorooctane sulphonic acid (PFOS), a surfactant PFAS, was found to be associated with higher levels of sex hormone-binding globulin (SHBG) and luteinising hormone but not testosterone in highly exposed men (Petersen *et al.*, 2018). PFAS were associated with increased odds of premature ovarian insufficiency in women (Zhang *et al.*, 2018) and with lower SHBG, follicle-stimulating hormone and testosterone in adolescents (Tsai *et al.*, 2015). In a study of contaminated drinking water supplies, PFOS was associated with lower oestradiol and testosterone in boys and with lower testosterone in girls, and perfluorooctanoic acid (PFOA), another surfactant PFAS, was associated with lower testosterone among boys (Lopez-Espinosa *et al.*, 2016).

Given the range of chemicals included in this review, a list of chemical abbreviations is provided in Table I.

Objectives

The aim of this systematic review was to summarise the strength of evidence for associations of POPs with couple fecundability (operationalised as TTP) and to identify gaps and limitations in the literature, with the goal of informing policy decisions and future research programs. Our systematic review focuses on chemicals targeted for elimination or restriction by the Stockholm Convention on Persistent Organic Pollutants (United Nations Environment Programme, 2008) (not currently ratified by the USA). Although the use and production of POPs are increasingly restricted, even chemicals that have been banned continue to impact human health because of their persistence in the environment and food chain. Understanding the association between POPs and TTP is important from a public health perspective not only because TTP is the main diagnostic indicator of couple infertility and subsequent use of assisted reproductive technologies, but also because of accumulating evidence that subfertility itself is associated with adverse health outcomes both for those attempting to conceive (Senapati, 2018; Choy and Eisenberg, 2020) and for their resulting children (Hwang *et al.*, 2018; Robinson *et al.*, 2020). Where the strength of evidence is limited, we highlight improvements in study design that will help guide future research and provide more conclusive results.

Methods

This review followed the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) statement (Moher *et al.*, 2009). The protocol is registered (CRD42019146534) on PROSPERO (www.crd.york.ac.uk/prospero) and we adhered to Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) (Moher *et al.*, 2015; Shamseer *et al.*, 2015).

Search strategy

A professional health sciences librarian (MK-F) developed and executed two bibliographic searches that were combined for the current review. The first search identified papers published between 1 January 2007 and 25 August 2017 in MEDLINE on the PubMed platform,

Table I Summary of chemicals and abbreviations.

Organochlorine (OC) pesticides
Aldrin
DDE: dichlorodiphenyldichloroethylene
DDT: dichlorociphenyltrichloroethane
Dieldrin
Endosulfan
HCB: hexachlorobenzene
HCH: hexachlorohexane
Heptachlor
Heptachlor epoxide
Mirex
Oxychlordane
Trans-nonachlor
Halogenated flame retardants
HBCDD: hexabromocyclododecane
PBBs: polybrominated biphenyls
PBDEs/BDEs: polybrominated diphenyl ethers
Polychlorinated organic compounds
PCBs: polychlorinated biphenyls
PCDFs: polychlorinated dibenzofurans
TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin)
PFAS: per- and polyfluoroalkyl substances
EtFOSAA: ethyl perfluorooctane sulphonamido acetic acid
MeFOSAA: methyl perfluorooctane sulphonamido acetic acid
PFDA: perfluorodecanoic acid
PFDeA: perfluordecanoic acid
PFDoDA: perfluorododecanoic acid
PFHpS: perfluoroheptane sulphonic acid
PFHxS: perfluorohexane sulphonic acid
PFNA: perfluorononanoic acid
PFOA: perfluorooctanoic acid
PFOS: perfluorooctane sulphonic acid
PFOSA: perfluorooctane sulphonamide
PFTrDA: perfluorotridecanoic acid
PFUnA/PFUnDA: perfluoroundecanoic acid

EMBASE.com, Global Health (OvidSP), DART (Developmental and Reproductive Toxicology)/TOXLINE (National Library of Medicine, US) and POPLINE (popline.org) (Hipwell *et al.*, 2019). In the second search, MK-F updated the strategy after checking for new controlled vocabulary terms and adding one deemed relevant, then searched the same five databases for articles published from 31 July 2017 until 6 August 2019. Dates covered overlapped slightly with the original search in order not to miss any added but not previously indexed articles. Subject thesaurus vocabulary (e.g. MeSH, EMTREE), text words and author keywords all contributed to both search builds with the exception of one MeSH term ('Heavy Metal Poisoning'), which was introduced in 2018 and therefore only included in the search update. Retrievals were limited to human studies in English. Animal, plant and soil fertility terms were removed before downloading to EndNote (Thomson Reuters). Duplicates among the new citations and from the original search were deleted. The full search strategy is reproduced in the Supplementary Table SI.

Screening and eligibility

Article screening was conducted with DistillerSR software (Evidence Partners, ON, Canada) using standardised forms for title and abstract screening and for full-text review. Each level of review (see Fig. 1) was completed in duplicate by authors L.G.K., K.G.H., E.L.S., Y.Z., P.F.-L., C.A.P. and A.E.H., and any conflicts were resolved through discussion.

At the title- and abstract-screening level, we included all human studies that related to any chemical exposure and TTP or fecundability and screened out editorials, opinion pieces, introductions to special sections or articles that described only lifestyle (e.g. caffeine, alcohol, illicit drugs, medication, stress) or clinical factors (e.g. semen parameters, IVF success, obesity). We obtained full-text reports for all titles that did not meet exclusion criteria or where there was any uncertainty about content. At the second (full text) level of screening, we included only original empirical research papers that considered TTP or fecundability as an outcome and examined exposure to persistent POPs, specifically: OC pesticides (DDT, DDE, aldrin, chlordane, chlordecone, dieldrin, endosulfan, endrin, heptaclor, hexachlorobenzene (HCB), HCH, lindane, mirex, toxaphene, PCP); BFRs (PBDEs, PBBs, hexabromocyclododecane (HBCDD)); PCBs (dioxins, furans); PFAS (PFOA, PFOS, perfluorononanoic acid (PFNA), perfluorohexane sulphonic acid (PFHxS)); other chemicals on the Stockholm Convention POPs list; and POPs in general. No *a priori* inclusion/exclusion criteria were applied according to how individuals were exposed (e.g. day-to-day activities or in the workplace) or according to study design (i.e. retrospective or prospective cohort, cross-sectional or case-control).

Data extraction

We created standardised forms for data extraction in DistillerSR, which were also completed in duplicate, and coding discrepancies were resolved through discussion. Where available, we reviewed prior articles that described study methods in greater detail. Review authors were not blind to article titles or authors. Once data had been extracted, characteristics of the papers reviewed were placed in Table III. Results of analyses for female and male chemical exposure were summarised in Tables IV and V, respectively. In some cases, data from the same study were analysed differently in separate publications. We elected to count only the primary paper as a distinct contribution to the literature, listing the results of the alternative or subgroup analyses underneath the main publication in Tables III and IV.

Risk of bias assessment

We used the Newcastle-Ottawa Scale (NOS) (Stang, 2010; Wells *et al.*, 2011; Zeng *et al.*, 2015) to assess risk of bias in three domains: participant selection/exposure, comparability of groups and outcome assessment (see Table II). High-quality study characteristics (associated with low risk of bias) were awarded a star with a maximum of one star for each numbered item within each domain. Because selection/exposure item 4 ('Demonstration that outcome, i.e. pregnancy, was not present at the start of the study') was not relevant for retrospective studies enrolling participants in the prenatal period or later, we

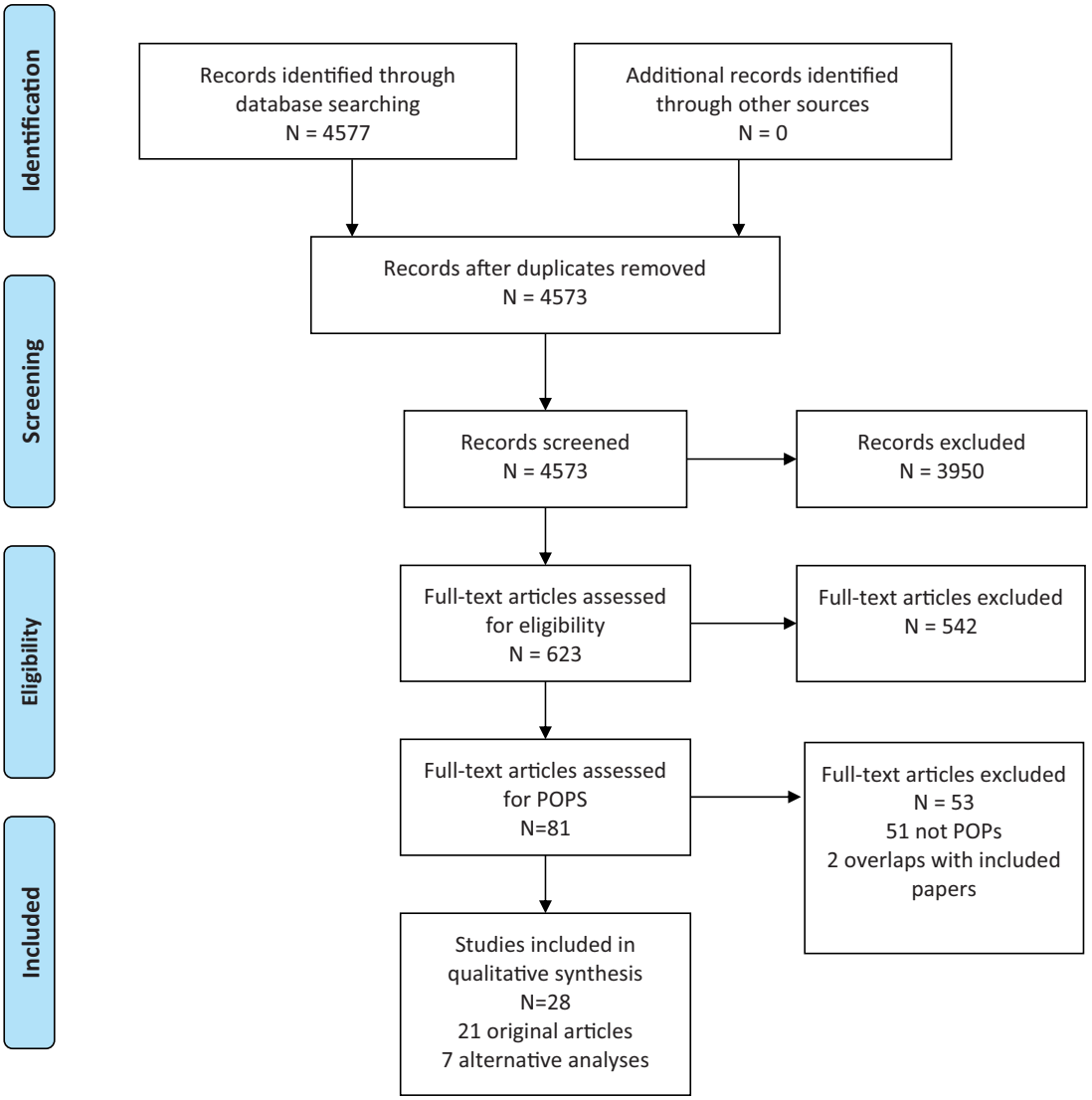

Figure 1. PRISMA flow chart.

replaced this item with 'Was exposure measured in women and men?', giving a star to studies that measured exposures in both partners. We followed recommendations to convert the NOS score to Agency for Healthcare Research and Quality (AHRQ) standards of good, fair and poor (Singh *et al.*, 2015). Specifically, good-quality studies were identified as those awarded 3–4 stars in the selection/exposure domain AND 1–2 stars in the comparability domain AND 2–3 stars in the outcome domain. Fair-quality studies were indicated by 2 stars for selection/exposure AND 1–2 stars for comparability AND 1–2 stars for outcome, whereas poor-quality studies scored 0–1 for selection/exposure OR 0 for comparability OR 0 for outcome.

The NOS criteria apply generally to epidemiological studies. However, several issues are particularly relevant to TTP studies examining persistent chemical exposures that were not captured by the NOS. Thus, we devised five additional quality metrics to identify specific methodological features of POP and fecundability studies that distinguish those of highest quality: (i) POP exposure was measured between 12 months preconception and 1 month postpartum; (ii) POP exposure was measured in blood; (iii) analyses were adjusted for blood lipids (except for PFAS analyses) or stratified by parity (for PFAS analyses); (iv) participants were actively trying to conceive; and (v) pregnancy status was assessed daily (Table II).

Most POPs are lipophilic. Nevertheless, depending on the causal relation among chemicals, lipids and outcome, adjustment for serum lipid concentrations may not always be necessary. Because the true causal relation is rarely known, however, lipid adjustment is commonly practiced and we therefore awarded studies that did so an extra quality point (#3) (except for those of PFAS, as stated above and explained below). The two prevalent methods for lipid adjustment are standardisation (dividing the chemical concentration by the lipid concentration) or including the lipid concentration in the statistical model as a covariate. Simulations have shown covariate adjustment to be less prone to bias than standardisation, but have also shown the validity of both

Table II Assessment of risk of bias and study quality.

Newcastle-Ottawa Scale domains	Criteria for higher quality
Selection	
Representativeness of exposed cohort or occupational group	Truly or somewhat representative of the population or occupational group*
Selection of the non-exposed cohort	Drawn from the same community or occupational group as the exposed cohort and over the same time period*
Adequacy of exposure measure	Independent, individual-level biological measure (e.g. blood, semen)*
Participants in whom exposure was measured	Women and men*
Comparability	
Comparability of cohorts on the basis of design (e.g. groups are matched on key variables) or control for confounders in analysis	Controlled for age*
	Controlled for at least one additional factor (e.g. body mass index, socioeconomic status, race or lifetyle factors such as smoking)*
Outcome	
Assessment of outcome	Independent, biological measure of pregnancy (e.g. home pregnancy test) OR medical record confirmation OR recruited when already pregnant (if retrospective design)*
Study design	Time to pregnancy measured prospectively OR recalled during pregnancy*
Completeness of outcome data	No missing outcome data OR complete follow-up (all subjects accounted for)*
Additional quality metrics	
1. Was exposure measured between 12 months preconception and one month postpartum?	Yes
2. Was exposure measured in blood?	Yes
3. For chemicals other than PFAS: Were blood lipids controlled for either by adjusting the exposure measure or by adding blood lipids to the regression model? For PFAS: Was analysis conducted in nulliparous women?	Yes
4. Were participants actively trying to conceive?	Yes
5. Was pregnancy status assessed with daily pregnancy tests?	Yes

*Study characteristics that were used to convert NOS scores to AHRQ standards of good, fair and poor.

methods to be vulnerable to error in lipid measurement, which may occur if non-fasting serum samples are used (Schisterman *et al.*, 2005).

As indicated above by the different criteria used to award the extra quality point #3 to analyses of PFAS, this group of chemicals has two features that distinguish it from other POPs and that require special consideration when examining associations between PFAS and TTP. PFAS are not lipophilic, so lipid adjustment is not necessary. In addition, serum PFAS concentrations generally decline during pregnancy (Kato *et al.*, 2014; Pan *et al.*, 2017) and are lower in parous compared to nulliparous women (Brantsæter *et al.*, 2013), likely as a result of transferring PFAS to the foetus during gestation and breastfeeding (Mondal *et al.*, 2014; Cariou *et al.*, 2015; Motas Guzmàn *et al.*, 2016). Causal diagrams have shown that the best way to avoid several potential sources of bias in analyses of PFAS and TTP is to restrict analyses to nulliparous women (Bach *et al.*, 2018). Therefore, we awarded PFAS studies the extra quality point #3 if they stratified by parity or restricted to nulliparous women.

TTP studies are inherently limited. On the one hand, retrospective studies, often conducted among women participating in pregnancy cohorts, lack data from couples who failed to conceive and from pregnancies that resulted in early miscarriage, and may be subject to biased recall of TTP (although over the short term, recalled TTP has been shown to have reasonable validity (Zielhuis *et al.*, 1992)). Additionally, retrospective studies measure exposure levels in samples collected after the outcome has occurred. In the case of non-persistent chemicals, where body burden can vary with day-to-day exposure, this is problematic, as urinary concentrations measured during pregnancy (often in a spot sample) may not accurately reflect preconception levels. For POPs, which are generally lipophilic and have half-lives of years, this is less concerning, although evidence suggests levels may vary due to physiologic changes across periconception, pregnancy and the postpartum period (Bloom *et al.*, 2007, 2009; Buck Louis *et al.*, 2019). While these studies have evaluated changes in absolute POP concentration over the course of pregnancy, they do not evaluate whether the rank order of POP concentration within their study populations varies. If the rank order is preserved, then results can be interpreted as associations between the relative concentrations of POPs and fecundity. As an example, although the absolute value of maternal blood lead concentration changes over the course of pregnancy, the intra-class correlations remain quite high, preserving the rank order and making interpretations viable. On the other hand, while prospective TTP studies are generalisable only to pregnancy planners, who likely differ from non-planners on a variety of factors, they are less likely to suffer other forms of bias and guarantee that exposure was measured prior to

Table III Study characteristics.

First author, year	Study name/ acronym	Country	Period of exposure	Sample/ study design	No. women	No. men	Measurement mode of chemical exposure			AHRQ rating/ additional quality points
							Serum	Plasma	Non-biological	
Bach, 2015a	ABC	Denmark	2008–2013	General/ retrospective	1372	0	PFAS: PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnA			Good/4
Bach, 2015b	DNBC	Denmark	1996–2002	General/ retrospective	1601	0		PFAS: PFOA, PFOS		Good/4
Fei, 2009 (smaller subset)					1240	0		PFAS: PFOA, PFOS		
Bach, 2018	Lifestyle During Pregnancy Study nested within the DNBC	Denmark	1996–2002	General/ retrospective	1251	0		PFAS: PFOS, PFOA, PFHxS, PFHpS, PFNA, PFDA		Good/4
Buck Louis, 2009	NYSACS	USA	1996–1997	Specialized[a]/ prospective	83	0	PCBs: total (76 congeners), oestrogenic, antioestrogenic			Good/4
Buck Louis, 2013	LIFE	USA	2005–2009	General/ prospective	501	501	PBB 153; OC pesticides: HCB, β HCH, γ-HCH, oxy-chlordane, trans-nonachlor, p,p′-DDT, o,p′-DDT, p,p′-DDE, mirex; PBDEs: BDE 17, 28, 47, 66, 85, 99, 100, 153, 154, 183; PCBs: PCB 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; PFAS: EtFOSAA, MeFOSAA, PFDeA, PFNA, PFOSA, PFOS, PFOA			Good/3.5
Lum, 2017 (reanalysis adjusting for cycle length)					501	0	PFAS: PFDeA, PFNA, PFOA, PFOS, PFOSA, EtFOSAA, MeFOSAA			
Hwang, 2019 (latent class reanalysis of joint male and female exposure)					401	401	PCB 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			
Zhang, 2019 (weighted kernel machine regression reanalysis of joint male and female exposure)					401	401	PCB 28, 66, 74, 99, 105, 118, 138, 146, 153, 156, 170, 180, 187, 194, 196, 201, 206, 209			

Continued

Table III Continued

First author, year	Study name/ acronym	Country	Period of exposure	Sample/ study design	No. women	No. men	Measurement mode of chemical exposure			AHRQ rating/ additional quality points
							Serum	Plasma	Non-biological	
Campagna, 2015		Italy	1946–1950	Specialized[b]/ retrospective	0	1223			DDT	Poor/0
Chevrier, 2013	PELAGIE	France	2002–2006	General/ retrospective	332	0	PCBs: PCB 74, 99, 101, 118, 138, 153, 170, 180, 183, 187, 194, 203, ΣPCBs; Organochlorine pesticides: α-HCH, β-HCH, y-HCH, HCB, heptachlor, heptachlor epoxide, aldrin, dieldrin, α-endosulfan, β-endosulfan, p,p'-DDE, p,p'-DDT, o,p'-DDE, o,p'-DDT; PBDEs: BDE 28, 47, 99, 100, 153, 154, 183, 209; PBB 153; HBCDD			Good/4
Cohn, 2011	CHDS	USA	1960–1963	General/ retrospective[c]	289	0	PCBs: PCB 66, 74, 99, 101, 105, 118, 138, 153, 156, 167, 170, 180, 183, 187, 201, 203			Fair/2
Gennings, 2013 (reanalysis of PCB mixtures using weighted quantile sum regression)					289	0	PCBs: PCB 56, 66, 74, 99, 101, 105, 118, 138, 146, 153, 156, 167, 170, 180, 183, 187, 201, 203			
Crawford, 2017	Time to Conceive	USA	2008–2009	General/ prospective	99	0	PFAS: PFOA, PFOS, PFNA, PFHxS			Fair/3
Eskenazi, 2010	SWHS	Italy	1976	Specialized[d]/ retrospective	278	0	TCDD			Good/3
Gao, 2016	LWBC	China	2010–2012	General/ retrospective	207	0	PBDEs: BDE 28, 47, 85, 99, 100, 153, 154, 183, ΣPBDE (28, 47, 99, 100, 153)			Good/3
Han, 2016	Fisheater Family Health Study	USA	1973–1991	Specialized[a]/ retrospective[c]	151	0	PCBs, p,p'-DDE			Poor/1
Harley, 2008	CHAMACOS	USA	1999–2000	Specialized[b]/ retrospective	402	0	p,p'-DDT, o,p'-DDT, p,p'-DDE			Good/4
Harley, 2010	CHAMACOS	USA	1999–2000	Specialized[b]/ retrospective	223	0	PBDEs: BDE 47, 99, 100, 153			Good/4
Jorgensen, 2014	INUENDO	Greenland, Poland, Ukraine	2002–2004	General/ retrospective	938	401	PFAS: PFOS, PFOA, PFHxS, PFNA			Good/4
Small, 2011		USA	1973–1974	Specialized[d]/ retrospective[c]	194	0	PBB 153			Poor/1

Continued

Table III Continued

First author, year	Study name/ acronym	Country	Period of exposure	Sample/ study design	No. women	No. men	Measurement mode of chemical exposure			AHRQ rating/ additional quality points
							Serum	Plasma	Non-biological	
Snijder, 2011	Generation R	Netherlands	2002–2006	General/ retrospective	2774	2728			Polychlorinated organic compounds, pesticides, flame retardants, any endocrine disruptors	Fair/2
Velez, 2015	MIREC	Canada	2008–2011	General/ retrospective	1743	0		PFAS: PFOS, PFOA, PFHxS		Good/3
Vestergaard, 2012	Danish First Pregnancy Planner Study	Denmark	1992–1995	General/ prospective	222	0	PFAS: PFOS, PFOA, PFHxS, PFNA, PFDA, MeFOSAA, EtFOSAA, PFOSA			Good/3
Whitworth, 2016	MoBa	Norway	2003–2004	General/ retrospective	451	0		PFAS: PFOSA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFHxS, PFHpS, PFOS		Good/4
Whitworth, 2012 (dichotomous TTP outcome only)					910	0		PFAS: PFOS, PFOA		
Ding, 2014 (reanalysis accounting for case-cohort sampling)					910	0		PFOA		
Yang, 2008	Yucheng	Taiwan	1979	General[d]/ retrospective	412	0			PCBs, PCDFs	Fair/2

[a]Anglers/fisheaters and spouses.
[b]Pesticide applicators/farmworkers and spouses.
[c]Prenatal exposure.
[d]Accidental exposure.
ABC, Aarhus Birth Cohort; DNBC, Danish National Birth Cohort; NYSACS, New York State Angler Cohort Study; LIFE, Longitudinal Investigation of Fertility and the Environment; PELAGIE, Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance; CHDS, Child Health and Development Studies; SWHS, Seveso Women's Health Study; LWBC, Laizhou Wan Birth Cohort; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; MIREC, Maternal-Infant Research on Environmental Chemicals; MoBa, Norwegian Mother and Child Cohort Study

Table IV Fecundability odds ratios in women.

First author, year	Study name/ acronym	Unit of analysis	Organochlorine pesticides	Brominated flame retardants (PBDEs and PBBs)	Polychlorinated organic compounds (PCBs, dioxins, and furans)	PFAS	Covariates
Bach, 2015a	ABC	Quartiles (Q4 vs Q1)				Nulliparous PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnA: ns	Age, prepregnancy BMI, education
		Continuous				Nulliparous PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA, PFUnA: ns	
Bach, 2015b	DNBC	Quartiles (Q4 vs Q1)				Nulliparous PFOS: FOR=0.79 [0.63, 0.99]	Age, prepregnancy BMI, SES, sample
						Parous PFOA: 0.76 [0.61, 0.94]	
		Continuous (ln)				Nulliparous PFOS: FOR=0.78 [0.63, 0.97]	
						Parous PFOA: 0.72 [0.61, 0.87]	
Fei, 2009 (smaller subset)		Quartiles (Q4 vs Q1)				Combined parity PFOA: FOR=0.60 [0.47, 0.76 and OR TTP >12 months=2.54 [1.47, 4.39]; PFOS: FOR=0.74 [0.58, 0.93 and OR TTP >12 months=1.77 [1.06, 2.95]	Maternal age, parity, prepregnancy BMI, SES, prepregnancy alcohol; paternal age, education
Bach, 2018	Lifestyle During Pregnancy Study nested within the DNBC	Quartiles (Q4 vs Q1)				Nulliparous PFHxS, PFHpS, PFOS, PFOA, PFNA, PFDA: ns	Age, prepregnancy BMI, SES
						Parous PFOA: FOR=0.79 [0.75, 0.83]; PFOS: FOR=0.69 [0.66, 0.73]; PFHxS: FOR= 0.71 [0.53, 0.94]; PFHpS: FOR=0.79 [0.58, 1.09]; PFNA: FOR=0.97 [0.93, 1.01]; PFDA: FOR=0.85 [0.82, 0.89]	Age, prepregnancy BMI, SES, interpregnancy interval
Buck Louis, 2009	NYSACS	Continuous (ln)			ΣPCBs: FOR=1.10 [1.00, 1.20]; ΣEstrogenic PCBs: FOR=0.32 [0.03, 3.89]; ΣAntioestrogenic PCBs: FOR=0.01 [<0.00, 1.99]; ΣOther PCBs: 1.44 [0.88, 2.37]		Serum lipids, frequency of intercourse, age, parity, smoking, alcohol
Buck Louis, 2013	LIFE	Continuous (log_SD)	HCB, β-HCH, γ-HCH, oxychlordane, trans-nonachlor, p,p'-DDT, o,p'-DDT, p,p'-DDE, mirex: ns	PBB 153: ns; BDE 17, 28, 47, 66, 85, 99, 100, 153, 154, 183: ns	PCB 118: FOR=0.82 [0.68, 0.98]; PCB 167: FOR=0.79 [0.64, 0.97]; PCB 209: FOR=0.82 [0.68, 0.99]	Combined parity PFOSA: FOR=0.82 [0.71, 0.95]	Left truncation, sum of all other chemicals in class, age, prepregnancy BMI, serum cotinine, site, lipids (except in PFAS models)

Continued

Table IV Continued

First author, year	Study name/ acronym	Unit of analysis	Organochlorine pesticides	Brominated flame retardants (PBDEs and PBBs)	Polychlorinated organic compounds (PCBs, dioxins, and furans)	PFAS	Covariates
Lum, 2017 (reanalysis adjusting for cycle length)		Tertiles (T3 vs T1)				Combined parity PFNA: OR=0.7 [0.3, 1.1]	Intercourse pattern, menstrual cycle length, age, prepregnancy BMI, smoking at enrolment, all other PFAS measured
Chevrier, 2013	PELAGIE	Tertiles (T3 vs T1)	β-HCH: FOR=0.61 [0.43, 0.86]; p,p'-DDE: FOR=0.60 [0.42, 0.84]; HCB: FOR=0.67 [0.48, 0.95]	BDE 209: ns	PCB 118: FOR=0.64 [0.45, 0.91]; PCB 138: FOR=0.57 [0.40, 0.81]; PCB 153: FOR=0.48 [0.33, 0.69]; PCB 170: FOR=0.64 [0.44, 0.91]; PCB 180: FOR=0.64 [0.44, 0.92]; PCB 187: 0.59 [0.40, 0.85]; ΣPCBs: FOR=0.46 [0.32, 0.66]		Age, prepregnancy BMI, smoking, oral contraceptive use, total lipids
		≥LOD vs <LOD	Heptachlor epoxide: FOR=0.76 [0.58, 1.00]		PCB 183: FOR=0.69 [0.52, 0.94]		
		Continuous (log10)	β-HCH: FOR=0.49 [0.29, 0.80]; p,p'-DDE: FOR=0.84 [0.71, 0.99]		PCB 118: FOR=0.42 [0.23, 0.75]; PCB 138: FOR=0.43 [0.22, 0.82]; PCB 153: FOR=0.37 [0.18, 0.74]; PCB 180: FOR=0.47 [0.23, 0.97]; PCB 187: FOR=0.63 [0.43, 0.91]; ΣPCBs: 0.39 [0.19, 0.78]		
Cohn, 2011	CHDS	Continuous (per SD)			PCB 99: FOR=0.75 [0.62, 0.91]; PCB 105: FOR=1.21 [1.04, 1.41]; PCB 138: FOR=1.99 [1.45, 2.75]; PCB 156: FOR=0.83 [0.71, 0.97]; PCB 183: FOR=1.21 [0.99, 1.48]; PCB 187: FOR=0.44 [0.28, 0.69]; (ΣPCB 99, 156, 187)/(ΣPCB 105, 138, 183): FOR=0.80 [0.70, 0.92]		All other PCB congeners, if mother breastfed, maternal race/ethnicity, lipids
		75th vs. 25th percentile			PCB 99: FOR=0.69 [0.53, 0.89]; PCB 105: FOR=1.44 [1.09, 1.91]; PCB 138: FOR=2.14 [1.50, 3.05]; PCB 156: FOR=0.78 [0.63, 0.96]; PCB 183: FOR=1.27 [0.99, 1.63]; PCB 187: FOR=0.59 [0.44, 0.79]; (ΣPCB 99, 156, 187)/(ΣPCB 105, 138, 183): FOR=0.62 [0.47, 0.83]		

Continued

Table IV Continued

First author, year	Study name/ acronym	Unit of analysis	Organochlorine pesticides	Brominated flame retardants (PBDEs and PBBs)	Polychlorinated organic compounds (PCBs, dioxins, and furans)	PFAS	Covariates
Crawford, 2017	Time to Conceive	Quartiles (Q4 vs Q1–3)				Combined parity PFOA, PFOS, PFNA, PFHxS: ns	Age, mean cycle length
Eskenazi, 2010	SWHS	Continuous (log10)			Measured TCDD: FOR=0.75 [0.60, 0.95; Extrapolated TCDD: FOR=0.73 [0.58, 0.94]		Maternal and paternal age,
		Quartiles (Q4 vs. Q1)			Measured TCDD: FOR=0.63 [0.42, 0.96]		parity, irregular menstrual cycle, OC use, smoking, history of gynaecologic or chronic health conditions
Gao, 2016	LWBC	Continuous (ln) then OR back-transformed		PBDE 28: OR TTP >12 months=1.34 [1.03, 1.76]			Maternal age, prepregnancy BMI, education, occupation, second-hand smoke, parity; paternal age, occupation, smoking, alcohol; family income
Han, 2016	Fisheater Family Health Study	>7.4 μg/L vs <2.5 μg/L	p,p'-DDE: ns		PCB: FOR=0.42 [0.20, 0.88]		Age, cohort, education
Harley, 2008	CHAMACOS	Continuous (log10)	p,p'-DDT, o,p'-DDT, p,p'-DDE: ns				Age, irregular menstrual cycle, hormonal contraceptive use, breastfeeding, history of gynaecologic conditions, caffeine, years in USA, maternal and paternal occupational pesticide exposure, home pesticide use, proximity of home to fields, trying to conceive
Harley, 2010	CHAMACOS	Continuous (log10)		BDE 100: FOR=0.61 [0.42, 0.89]; BDE 153: FOR=0.52 [0.33, 0.81]; ΣPBDEs: FOR=0.68 [0.47, 0.98]			Age, years in USA, history of gynaecologic conditions, hormonal contraceptive use, breastfeeding, caffeine, pesticide, exposure

Continued

Table IV Continued

First author, year	Study name/ acronym	Unit of analysis	Organochlorine pesticides	Brominated flame retardants (PBDEs and PBBs)	Polychlorinated organic compounds (PCBs, dioxins, and furans)	PFAS	Covariates
Jorgensen, 2014	INUENDO	Tertiles (T3 vs T1)				Nullipaorus PFOA, PFOS, PFHxS, PFNA: ns	Age, smoking, prepregnancy BMI, gestational week of blood sampling (country for pooled analyses)
						Combined parity PFNA Greenland: FOR=0.71 [0.54, 0.94] and OR TTP >12 months=2.15 [1.05, 4.42]	Age, smoking, parity, prepregnancy BMI, gestational week of blood sampling (country for pooled analyses)
		Continuous (log10)				Nulliparous PFOA Ukraine: FOR=1.46 [1.02, 2.08]; PFOA pooled sample: FOR=1.31 [1.03, 1.68]	Age, smoking, prepregnancy BMI, gestational week of blood sampling (country for pooled analysis)
						Combined parity PFNA Greenland: FOR=0.72 [0.58, 0.89] and OR TTP >12 months=1.97 [1.22, 3.19]; PFNA pooled sample: FOR=0.80 [0.69, 0.94] and OR TTP >12 months=1.53 [1.08, 2.15]	Age, smoking, parity, prepregnancy BMI, gestational week of blood sampling (country for pooled analysis)
Small, 2011		Tertiles (LOD and median split above LOD)		PBBs: ns			None
Snijder, 2011	Generation R	Occupational exposure (y/n)	Any pesticides, occupational: ns	Occupational: ns	Occupational: ns		Age
Velez, 2015	MIREC	Continuous (log_SD)				Combined parity PFOA: FOR=0.89 [0.83, 0.94], OR TTP >12 months=1.31 [1.11, 1.53]; PFOS: FOR=0.96 [0.91, 1.02], OR TTP >12 months=1.14 [0.98, 1.34]; PFHxS: FOR=0.91 [0.86, 0.97], OR TTP >12 months=1.27 [1.09, 1.48]	Age, prepregnancy BMI
Vestergaard, 2012	Danish First Pregnancy Planner Study	Continuous (ln)				Nulliparous PFOS: FOR=1.39 [0.92, 2.09]; PFHxS: FOR=1.33 [1.01, 1.75]; EtFOSAA: FOR=0.79 [0.62, 1.00]	Female age, prepregnancy BMI, smoking, length of menstrual cycle, female diseases affecting fecundability, oligospermia

Continued

Table IV Continued

First author, year	Study name/ acronym	Unit of analysis	Organochlorine pesticides	Brominated flame retardants (PBDEs and PBBs)	Polychlorinated organic compounds (PCBs, dioxins, and furans)	PFAS	Covariates
Whitworth, 2016	MoBa	Interquartile range				Nulliparous PFOSA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFHxS, PFHpS, PFOS: ns	Age, prepregnancy BMI
Whitworth, 2012 (dichoto-mous TTP outcome only)		Quartiles (Q4 vs Q1)				Nulliparous: ns	Age, prepregnancy BMI, prepregnancy alcohol (latter for PFOA only)
						Parous PFOA: OR TTP >12 months=2.1 [1.0, 4.4]; PFOS: OR TTP >12 months=2.1 [1.2, 3.9]	
Yang, 2008	Yucheng	Exposed vs unexposed			PCBs/PCDFs: FOR = 0.90 [0.80–1.00], OR TTP >12 months=2.34 [1.23, 4.59]		Maternal age, paternal age, frequency of intercourse

ABC, Aarhus Birth Cohort; DNBC, Danish National Birth Cohort; NYSACS, New York State Angler Cohort Study; LIFE, Longitudinal Investigation of Fertility and the Environment; PELAGIE, Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance; CHDS, Child Health and Development Studies; SWHS, Seveso Women's Health Study; LWBC, Laizhou Wan Birth Cohort; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; MIREC, Maternal-Infant Research on Environmental Chemicals; MoBa, Norwegian Mother and Child Cohort Study.

Table V Fecundability odds ratios in men.

First author, year	Study name/ acronym	Unit of analysis	Organochlorine pesticides	Brominated flame retardants (PBDEs and PBBs)	Polychlorinated organic compounds (PCBs, dioxins, and furans)	PFAS	Covariates
Buck Louis, 2013	LIFE	Continuous (log_SD)	p,p'-DDE: FOR=0.83 [0.70, 0.97]	PBB 153: ns; BDE 17, 28, 47, 66, 85, 99, 100, 153, 154, 183: ns	PCB 101: FOR=1.28 [1.09, 1.51]; PCB 138: FOR=0.71 [0.52, 0.98]; PCB 156: FOR=0.77 [0.62, 0.96]; PCB 157: FOR=0.83 [0.70, 0.97]; PCB 167: FOR=0.82 [0.70, 0.96]; PCB 170: FOR=0.74 [0.56, 0.98]; PCB 172: FOR=0.82 [0.68, 0.99]; PCB 180: FOR=0.81 [0.66, 1.00]; PCB 209: FOR=0.78 [0.65, 0.94]	Combined parity EtFOSAA, MeFOSAA, PFDeA, PFNA, PFOSA, PFOS, PFOA: ns	Left truncation, sum of all other chemicals in class, age, BMI, serum cotinine, site, lipids (except in PFAS models)
Campagna, 2015		Occupational exposure (direct, indirect, unexposed)	DDT: ns				None
Jorgensen, 2014	INUENDO	Tertiles (T3 vs T1)				Combined parity PFOA, PFOS, PFHxS, PFNA: ns	Paternal and maternal age, paternal BMI
		Continuous (log10)				Combined parity PFNA Greenland: FOR=0.70 [0.50, 0.99]	
Snijder, 2011	Generation R	Occupational exposure (y/n)	Any pesticides, occupational: ns	Occupational: ns	Occupational: ns		Age

LIFE, Longitudinal Investigation of Fertility and the Environment.

outcome. To indicate these benefits, we chose to award the NOS study design quality point to prospective studies or those that measured retrospective TTP during pregnancy, when recall may still be considered reliable. We also awarded one of our additional quality points (#4) exclusively to prospective studies.

Results

Our search returned 4573 potentially relevant journal articles, of which 3950 were removed at the title and abstract-screening level. Of the remaining 623 full-text articles assessed for eligibility, 595 met study exclusion criteria, ultimately yielding 28 articles from 19 different studies (Fig. 1). Of these, 21 papers contained original analyses and seven employed alternative sampling or analytic techniques to analyse data presented in the primary papers (Fei *et al.*, 2009; Whitworth *et al.*, 2012; Gennings *et al.*, 2013; Ding *et al.*, 2014; Lum *et al.*, 2017; Hwang *et al.*, 2019; Zhang *et al.*, 2019). We present results from each alternative approach alongside the corresponding original analysis; together they are counted as one paper for the purposes of this systematic review. We excluded two publications that restated or summarised results that were already contained in the original articles. The reviewing team achieved good preliminary pairwise agreement in selecting articles for inclusion (weighted overall kappas for full-text review and for selection of chemicals = 0.73 and 0.98, respectively).

Description of studies

Characteristics of the 28 papers (21 primary, 7 alternative analyses) and 19 studies that provided results for this review are summarised in Table III. Studies were conducted in Europe (n = 9), North America (n = 7) and East Asia (n = 3). The California-based Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study (Harley *et al.*, 2008, 2010) and the Danish National Birth Cohort (DNBC) (Bach *et al.*, 2015b, 2018) each contributed two primary papers on different POPs. Twelve studies recruited participants from the general population and the remaining seven recruited from specialised populations, including communities of anglers and fish eaters (Buck Louis *et al.*, 2009; Han *et al.*, 2016), pesticide applicators (Campagna *et al.*, 2015), farmworkers (Harley *et al.*, 2008, 2010) and women who had been accidentally exposed through large-scale poisoning incidents (Yang *et al.*, 2008; Eskenazi *et al.*, 2010; Small *et al.*, 2011). Four studies recruited during the preconception period and measured TTP prospectively (the New York State Angler Cohort Study (NYSACS, Buck Louis *et al.*, 2009)), the LIFE study (Buck Louis *et al.*, 2013; Lum *et al.*, 2017), Time to Conceive (Crawford *et al.*, 2017) and the Danish First Pregnancy Planner Study (Vestergaard *et al.*, 2012)). Three of the retrospective TTP studies had data on the participants' own prenatal exposure (Cohn *et al.*, 2011; Small *et al.*, 2011; Han *et al.*, 2016). Among the three studies that did not have biological measures, exposure was assessed by means of employment records (Campagna *et al.*, 2015), self-reported occupation linked to a job-exposure matrix (Snijder *et al.*, 2011) and inclusion in a victims' registry (Yang *et al.*, 2008). Several papers analysed data from historic cohorts, the earliest of which assessed exposures between 1946 and 1950 (Campagna *et al.*, 2015), while others focused on more contemporary cohorts, the most recent of which concluded exposure data collection between 2011 and 2013 (Bach *et al.*, 2015a; Velez *et al.*, 2015; Gao *et al.*, 2016). Analytic sample sizes ranged from 83 (Buck Louis *et al.*, 2009) to 2774 (Snijder *et al.*, 2011) participants. While most analyses focused only on TTP in relation to the female partner's exposure, three papers reported results for both female and male partners (Snijder *et al.*, 2011; Buck Louis *et al.*, 2013; Jorgensen *et al.*, 2014), and one focused exclusively on males (Campagna *et al.*, 2015).

A note on effect sizes

In most cases, studies reported effect sizes as fecundability odds ratios (FORs) with 95% confidence intervals (CIs), modelling TTP as discrete, time-to-event data in months or menstrual cycles. Analogous to a hazard ratio, a FOR represents the probability of conceiving in a specified time period (month or cycle), conditional on not having conceived in the prior time period, per unit of chemical exposure. However, because different units of exposure were used, it is difficult to compare FORs across studies. Researchers frequently examined chemical exposure as a continuous variable, either on the arithmetic or logarithmic scale, and two studies analysed log-transformed chemical concentrations and then rescaled by the standard deviation (SD) to estimate the FOR per SD increase in the log chemical concentration (Buck Louis *et al.*, 2013; Velez *et al.*, 2015). One analysis calculated the FOR based on an interquartile range difference (Whitworth *et al.*, 2016) and another based on an SD difference (Cohn *et al.*, 2011). Alternatively or in addition, researchers modelled exposures categorically, comparing the probability of conception in the sample-specific highest tertile (T3) or quartile (Q4) to the lowest (T1 or Q1) in those with exposure greater than or equal to the limit of detection (LOD) versus below the LOD, or in other categories based on the distribution of their exposure data (Tables IV and V). In studies with non-biological exposure assessment, such as accidental poisoning, the FOR represents the per-month/cycle probability of conception in the exposed group relative to a non-exposed comparison group. A number of papers reported both FORs and odds ratios (ORs) for infertility, defined as TTP >12 versus ≤12 months, and used logistic regression to calculate ORs per unit change in chemical exposure (Tables IV and V). In general, diminished fecundability, or longer TTP, is indicated by an FOR <1 (reduced probability of conception in a given month/cycle) or an OR for infertility >1 (greater odds of taking more than 12 months to conceive).

Associations of female exposure to organochlorine pesticides with TTP

Among the five papers that examined associations of female exposure to OC pesticides with TTP, one was conducted in a prospective study and the others were conducted in retrospective studies. One of the retrospective studies was intergenerational and consisted of women's retrospective report of TTP within a long-term prospective study that began during or shortly after their mothers' pregnancy. Mothers' serum p,p′-DDE levels were extrapolated to approximate exposure during the time they were pregnant with their daughters, who eventually reported their own TTP (Han *et al.*, 2016).

Evidence for no association with TTP

The prospective LIFE study measured chemical concentrations in preconception serum samples of 501 couples in Michigan and Texas who were discontinuing contraception. The female partners tracked their menstrual cycles, days of sexual intercourse and various other

behaviours until pregnancy was achieved or 12 cycles had been completed (Buck Louis *et al.*, 2013). Exposure to β-HCH, γ-HCH, oxychlordane, trans-nonachlor, p,p′-DDT, o,p′-DDT, p,p′-DDE or mirex was not associated with TTP in unadjusted models. HCB was associated with longer TTP (FOR = 0.87 (0.77, 0.998)), but when adjusted for relevant covariates, serum lipids and site, the point estimate approached the null. In an analysis of 402 participants from the CHAMACOS study, which recruited pregnant women from five prenatal clinics that serve a low-income, predominantly farmworker population in California, neither p,p′-DDT, o,p′-DDT nor p,p′-DDE measured in late second-trimester serum was associated with self-reported TTP when modelled continuously with covariate adjustment (Harley *et al.*, 2008). Both the LIFE and CHAMACOS studies were rated 'good' on the NOS/AHRQ scale and met 3.5 and four of the five additional quality metrics, respectively. Prenatal exposure of 151 women to p,p′-DDE, extrapolated from measurements taken when their mothers participated in a cohort study of Michigan female anglers and fish eaters between 1973 and 1991 (in most cases postnatally), was not associated with self-reported TTP when they attempted to conceive decades later (Han *et al.*, 2016). This analysis ranked 'poor' on the NOS/AHRQ scale and, among other limitations, did not include lipid adjustment. Finally, a large retrospective analysis among 2774 participants in the population-based Generation R Study, a multiethnic prospective cohort study in Rotterdam, the Netherlands, that recruited women in early pregnancy between 2002 and 2006, yielded no association between possible or probable occupational exposure to pesticides in the preconception window, calculated according to a job-exposure matrix, and TTP (Snijder *et al.*, 2011). This study was rated 'fair' on the NOS/AHRQ scale and met two additional quality metrics but could not distinguish between OCs and other classes of pesticides.

Evidence for longer TTP

Seven out of 14 OC pesticides measured in the cord blood serum of 332 participants in the French Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (PELAGIE) study were detected in >10% of the samples and analysed in relation to TTP self-reported in the first half of pregnancy (Chevrier *et al.*, 2013). β-HCH and p,p′-DDE were associated with longer TTP when the exposures were modelled both as log10-transformed variables (FOR = 0.49 (0.29, 0.80) and 0.84 (0.71, 0.99), respectively) and when categorised into tertiles (T3 vs. T1: FOR = 0.61 (0.43, 0.86) and 0.60 (0.42, 0.84), respectively). HCB was also associated with longer TTP in the tertile model (FOR = 0.67 (0.48, 0.95)), as was heptachlor epoxide when dichotomised at the LOD (FOR = 0.76 (0.58, 1.00)). This study was rated 'good' on the NOS/AHRQ scale and met all of the additional quality metrics except daily pregnancy tests.

Weight of evidence

The majority of studies indicate no association between female exposure to OC pesticides and TTP. Although the PELAGIE study reported an association between higher female OC pesticide concentration and longer TTP, chemical levels were measured in cord serum, which may not be an accurate proxy of maternal periconceptional exposure. While wet-weight cord and maternal blood concentrations of OC pesticides measured in close proximity are positively correlated (Dewan *et al.*, 2013; Sexton *et al.*, 2013), levels are generally lower in cord blood. Furthermore, as serum lipid levels increase across pregnancy, lipid-adjusted concentrations decrease (Vizcaino *et al.*, 2014; Fisher *et al.*, 2016), even when wet-weight concentrations increase (Adetona *et al.*, 2013). The PELAGIE study adjusted for lipids, but did not account for length of gestation, which could confound the relation between OC pesticide concentration and TTP. Longer TTP is associated with preterm birth (Joffe and Li, 1994), which was not an exclusion criterion for the analysis. Results of this analysis may also be influenced by selection bias, as sampling is conditioned on cord blood availability (i.e. live birth), and longer TTP (Joffe and Li, 1994) and exposure to DDT (Eskenazi *et al.*, 2009) and HCH (Pathak *et al.*, 2010) are all associated with miscarriage. Two other studies of comparable quality found no associations for female OC pesticide exposure and TTP (Harley *et al.*, 2008; Buck Louis *et al.*, 2013), including the LIFE study, which assessed a similar array of chemicals in preconception serum samples.

Associations of female exposure to brominated flame retardants with TTP

Female exposure to BFRs, including PBBs and PBDEs, was analysed in six cohorts. While most studies assessed exposure during pregnancy and reported TTP retrospectively, the prospective LIFE study measured exposure to PBBs and PBDEs in preconception blood samples, while a study of female offspring of women exposed to high levels of PBBs through accidental contamination of agricultural products in Michigan assessed prenatal exposure and recalled TTP.

Evidence for no association with TTP

In 1973, a majority of Michigan residents were exposed to extremely high levels of PBB when Firemaster, a toxic flame retardant comprising 18 PBB congeners, was mistakenly sold to farmers throughout the state. Approximately 4000 residents were enrolled in long-term health monitoring, and they and their offspring continue to be followed. Small *et al.* (2011) analysed self-reported first-pregnancy TTP, dichotomised as ≤12 months versus >12 months, among daughters who had potential *in utero* PBB exposure. PBB concentrations around the time of the daughters' conception were extrapolated by applying a decay model to levels in maternal serum samples collected shortly after the incident. No association was found between PBB levels and odds of TTP >12 months. This study received a 'poor' NOS/AHRQ rating, in part because the authors did not control for any covariates in their analysis, and only met one of the additional quality metrics. The prospective LIFE study, which measured concentrations of PBB 153 and 10 PBDE congeners in preconception serum, found no statistically significant associations with continuous TTP (Buck Louis *et al.*, 2013). A similar result was found in the PELAGIE study, which measured PBB 153 and eight PBDE congeners, but only analysed BDE 209 in relation to recalled TTP, as the others were detectable in <10% of samples (Chevrier *et al.*, 2013). Investigators from the Generation R Study also reported no association between occupational exposure to flame retardants and retrospective TTP (Snijder *et al.*, 2011).

Evidence for longer TTP

The Chinese Laizhou Wan Birth Cohort (LWBC) includes women who were recruited when admitted for delivery from a county hospital in an area of Shandong Province that contains numerous BFR factories. In an

analysis of data from 207 participants, BDE 28 was associated with greater odds of self-reported TTP >12 months (OR = 1.34 (1.03, 1.76)) (Gao et al., 2016). This study received a 'good' NOS/AHRQ rating and met three out of five additional quality metrics. In the Californian CHAMACOS study, late second-trimester serum levels of BDE 100 and 153 were associated with longer recalled TTP (FOR = 0.61 (0.42, 0.89) and 0.52 (0.33, 0.81), respectively) as was the sum of the four PBDE congeners (BDEs 47, 99, 100 and 153) that were detected in >75% of samples (FOR = 0.68 (0.47, 0.98)) (Harley et al., 2010).

Weight of evidence

Although the majority of female BFR exposure analyses reported null results, two high-quality papers reported positive associations between PBDEs and TTP. Both the Chinese LWBC and Californian CHAMACOS studies sampled populations that were exposed to high levels of BFRs relative to most of the other studies identified in the systematic review. The majority of PBDE production is not restricted in China, although levels have been declining since production and use of pentaBDEs (e.g. BDEs 85, 99, 100) was phased out in 2007. Nevertheless, they still remain elevated in Shandong Province, where the LWBC recruited participants (Ma et al., 2017). Between 1975, when California adopted Technical Bulletin 117, which required the use of chemical flame retardants in upholstered furniture, and 2003, when the state banned the manufacture and sale of pentaBDEs and octaBDEs (e.g. BDEs 196, 197, 203), levels of PBDEs in pregnant women were among the highest worldwide (Zota et al., 2011). CHAMACOS participants were recruited between 1999 and 2000. By contrast, the LIFE study enrolled participants between 2005 and 2009, following the 2004 nationwide US ban of both pentaBDEs and octaBDEs. Apart from the UK and Ireland, European countries never required furniture to be impregnated with chemical flame retardants, so levels in countries such as France and the Netherlands, where the PELAGIE and Generation R studies recruited, were never as high as China or the USA. Further research is needed to explore the potential dose-dependence of associations between BFRs and TTP, as there is no *a priori* reason to expect transportability of estimates given how tied to place and time POP exposure levels and their covariates of interest are, and to investigate effects of novel BFRs that have been introduced in the wake of PBDE regulations.

Associations of female exposure to polychlorinated organic compounds with TTP

Seven out of eight studies that measured female exposure to polychlorinated organic compounds, including PCBs, dioxins and furans, reported associations with TTP, although not in consistent directions. These included both prospective and retrospective studies in both general and specialised populations, including two studies with prenatal exposure data.

Evidence for no association with TTP

The only study to report no association between PCBs and TTP was the Generation R Study, which estimated exposure based on occupational exposure in the preconception period (Snijder et al., 2011).

Evidence for longer TTP

Both prospective TTP studies that assessed PCB exposure reported longer TTP for at least some PCB congeners. The NYSACS analysis included 83 women from the larger study who indicated upon enrolment that they were considering or undecided about future pregnancies and who, when re-contacted 5 years later, were discontinuing contraception during the substudy recruitment period. Blood samples were collected during the baseline visit, and women tracked their menstrual cycles, as well as their sexual intercourse and various other behaviours until they tested positive for pregnancy or completed 12 cycles without conceiving. A total of 76 PCB congeners were assayed and entered into models summed and in groups based on purported biologic activity: 'estrogenic', 'antioestrogenic' and 'other' (Buck Louis et al., 2009). The point estimates for the sums of both oestrogenic and antioestrogenic congeners indicated a non-significant association with longer TTP (FOR = 0.32 (0.03, 3.89) and 0.01 (<0.00, 1.99), respectively). The wide confidence intervals reflect the small sample size, the fact that the three biological groups were entered into the same model, and the inclusion of a number of additional covariates. This study received a 'fair' NOS/AHRQ rating but met four out of five additional quality criteria. The larger and similarly designed LIFE study assayed 36 PCB congeners, of which three were associated with longer TTP in covariate-adjusted models (FOR_{PCB118} = 0.82 (0.68, 0.98), FOR_{PCB167} = 0.79 (0.64, 0.79) and FOR_{PCB209} = 0.82 (0.68. 0.99)), although two of them (PCBs 167 and 209) were detectable in only 25% and 23% of samples, respectively (Buck Louis et al., 2013).

Although the PELAGIE study enrolled women mid-pregnancy and measured chemicals in cord serum, the results were similar (Chevrier et al., 2013). PCBs 118, 138, 153, 170, 180, 183 and 187 were all associated with longer TTP when modelled continuously and/or categorically. The sum of all nine congeners that were detectable in >10% of samples was associated with longer TTP both in covariate-adjusted models that compared the highest to lowest tertiles and in models that examined continuous log10-transformed concentrations (FOR = 0.46 (0.32, 0.66) and 0.39 (0.19, 0.78), respectively).

Two historic cohorts with second-generation follow-up that assessed prenatal PCB exposure found associations with longer TTP in daughters. The Child Health and Development Studies (CHDS) analysis, which included 289 daughters born to women who had enrolled in the original study between 1960 and 1963 in Oakland, CA, assayed 16 PCB congeners in maternal serum collected 1–3 days postpartum (Cohn et al., 2011). Maternal PCBs 99, 156 and 187 were associated with longer retrospectively reported TTP in daughters in both continuous and categorical models jointly adjusted for all other PCBs, lipids and covariates. This study received an NOS/AHRQ rating of 'fair' and met two additional quality metrics. The CHDS data were reanalysed by Gennings et al. using non-linear weighted quantile sum regression to identify which congeners among the mixture of PCBs were most strongly associated with either longer or shorter TTP. They found that dioxin-like, antioestrogenic congeners (66, 74, 105, 118, 156 and 167) and two congeners not included in the original analysis and not classified according to proposed biological mechanism (56 and 146) were associated with longer TTP, as were the highly chlorinated PCBs (56, 101, 105, 146, 156, 167, 183 and 201) (Gennings et al., 2013).

In the other historic cohort, the Michigan Fisheater Family Health Study, in which PCB concentrations taken in serum samples collected at the time of initial enrolment were extrapolated to approximate

exposure around the time of the daughters' conception, the sum of PCB concentrations based on the Aroclor 1260 standard was divided into three categories (Han *et al.*, 2016). Women with periconceptional exposure in both the middle and high concentration groups had longer recalled TTP compared to the referent group (FOR = 0.50 (0.36, 0.99) and 0.42 (0.20, 0.88), respectively).

Finally, two landmark studies of accidental exposure to polychlorinated organic compounds also reported longer TTP. The Seveso Women's Health Study (SWHS) followed female residents of the region surrounding Seveso, Italy, where a chemical plant explosion in 1976 resulted in the highest exposure known in human residential populations to dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, TCDD), the most toxic compound in the chemical class. Participants who were age 0–40 years at the time of the explosion and provided serum samples between 1976 and 1980 were recruited to a follow-up study in 1996. Among the 278 who delivered a live birth that was intentionally conceived in the interim, serum dioxin concentration was measured in archived samples and extrapolated to approximate exposure at the time of conception, an interval that averaged 9 years (Eskenazi *et al.*, 2010). Concentrations shortly after the accident were associated with longer recalled TTP in both a covariate-adjusted continuous model and a model comparing the highest to lowest quartile (FOR = 0.75 (0.60, 0.95) and 0.63 (0.42, 0.96), respectively). Results were similar when extrapolated concentrations were used, although the 95% CI for the categorical model included the null value. This study received a 'good' NOS/AHRQ rating and met three additional quality metrics.

In 1979, an accidental poisoning incident occurred in central Taiwan, where more than 2000 people consumed cooking oil contaminated with PCBs which, when heated, produced toxic polychlorinated dibenzofurans (PCDFs) causing symptoms of 'oil disease' ('Yu-cheng' in Chinese). In a 2003 follow-up study, researchers analysed data from 186 married women from the Yucheng cohort who were age 25–45 years (infancy through 20 years old at the time of the accident) and had become pregnant after the period of exposure and 226 unexposed women who had lived near the registry members (Yang *et al.*, 2008). Those in the Yucheng cohort took longer to conceive their first pregnancy than those in the reference cohort (FOR = 0.90 (0.80, 1.00)) and had higher odds of TTP >12 months (OR = 2.34 (1.23, 4.59)). This study received a 'fair' NOS/AHRQ rating and met two additional quality criteria.

Evidence for shorter TTP

While both the NYSACS and CHDS papers reported longer TTP for some PCB congeners, they found that others were associated with shorter TTP. Specifically, the sum of all 76 PCB congener concentrations measured in preconception serum in the NYSACS was negatively associated with TTP (FOR = 1.10 (1.00, 1.20)), driven by PCBs in the non-oestrogenic, non-antioestrogenic category (Buck Louis *et al.*, 2009). In the CHDS, concentrations of PCBs 105, 138 and 183 in maternal postpartum serum were associated with shorter TTP in both continuous and categorical models jointly adjusted for all other PCBs, lipids and covariates (Cohn *et al.*, 2011). In a non-linear weighted quantile sum mixture analyses of the CHDS data, the dioxin-like, antioestrogenic congeners (PCBs 66, 74, 105, 118, 156 and 167) were associated with shorter TTP (Gennings *et al.*, 2013).

Weight of evidence

The nearly consistent results of seven out of eight studies of vastly different design that were conducted in disparate geographic locations and temporal periods, and in populations with widely varying ranges of exposure lend support to a link between female exposure to most polychlorinated organic compounds and reduced fecundability. Exceptions must be noted, however. Both the NYSACS and the CHDS reported that female concentrations of certain PCB congeners were associated with increased fecundability. Similarly, the LIFE study's finding that PCB 101 was associated with shorter TTP in contrast to several other PCBs that were associated with longer TTP implies that the stereochemical differences among various congeners may cause them to act via different biological mechanisms, sometimes resulting in opposing effects.

Associations of female exposure to polyfluoroalkyl substances with TTP

Nearly every paper identified by this systematic review and published since 2012 has examined PFAS in relation to TTP, indicating the growing attention being paid to this class of POPs, the use of which is just beginning to be regulated. Five retrospective and three prospective studies analysed female exposure to these chemicals and TTP, yielding nine primary articles, as the DNBC and Norwegian Mother and Child Cohort Study (MoBa) studies each published two papers on PFAS.

Evidence for no association with TTP

Nearly all of the analyses that reported no associations between female PFAS exposure and TTP were conducted in nulliparous women, as recommended. In the Danish Aarhus Birth Cohort (ABC), 16 PFAS were measured in stored serum samples collected between 9 and 20 weeks gestation in 1372 nulliparous participants with planned pregnancies. Among the seven PFAS that had detectable levels in ≥50% of samples, none was associated with TTP (Bach *et al.*, 2015a). In an analysis that included 1251 women with early pregnancy plasma PFAS measures and TTP information nested within the equally high-ranking DNBC, results were stratified by parity and no associations were observed among nulliparous women (Bach *et al.*, 2018). The multisite INUENDO study reported no difference in TTP comparing the highest tertile to the lowest of four PFAS (PFOA, PFOS, PFHxS and PFNA) measured in prenatal serum samples in nulliparous women from Greenland, Poland and Ukraine, as well as all three countries combined (Jorgensen *et al.*, 2014). In addition, an analysis of a subsample of nulliparous participants from the MoBa study that assessed fecundability in relation to 10 different PFAS (Whitworth *et al.*, 2016) found no associations, replicating the results of a prior analysis of nulliparous women from the same cohort in which odds of TTP >12 months was used as an outcome (Whitworth *et al.*, 2012). All four of these European studies received a 'good' NOS/AHRQ rating and met four out of five extra quality criteria.

The North Carolina Time to Conceive study recruited women attempting to become pregnant, collected preconception serum samples and had participants track their menstrual cycles, intercourse and other behaviours in a daily diary for up to 6 months (Crawford *et al.*, 2017). Among 99 participants with serum PFAS measures, there was no association of PFOA, PFOS, PFNA or PFHxS with TTP in either cycle-specific or day-specific models. Following a test for effect

modification by parity, which was not statistically significant, the authors chose not to stratify by or adjust for parity in their analysis.

Evidence for longer TTP

Two analyses of nulliparous women reported associations between PFAS and longer TTP. The Danish First Pregnancy Planner Study enrolled 430 couples trying to conceive and followed them for up to 6 months. Female participants provided preconception serum samples, 222 of which were available for chemical analysis (Vestergaard *et al.*, 2012). Among the several PFAS and PFAS metabolites assayed, only log-transformed ethyl perfluorooctane sulphonamido acetic acid (EtFOSAA) was associated with longer TTP (FOR = 0.79 (0.62, 1.00)). In an analysis of two randomly selected subsamples from the DNBC (n = 440 and 1161), PFOS and PFOA were measured in mid-pregnancy plasma around the same time participants were asked to recall their TTP (Bach *et al.*, 2015b). When pooled and stratified by parity, an association was observed between PFOS and longer TTP in both categorical (highest vs. lowest quartile) and continuous (ln-transformed) models among nulliparous women (FOR = 0.79 (0.63, 0.99) and 0.78 (0.63, 0.97), respectively). Results were similar for parous women. A prior unstratified analysis among 1240 participants in the same cohort that adjusted for parity found both reduced fecundability and increased odds of TTP >12 months when comparing highest to lowest quartiles of PFOA (FOR = 0.60 (0.47, 0.76), OR = 2.54 (1.47, 4.39)) and PFOS (FOR = 0.74 (0.58, 0.93), OR=.77 (1.06, 2.95)) (Fei *et al.*, 2009).

Two studies that performed their analyses in samples that combined parous and nulliparous women and did not adjust for parity reported positive associations between PFAS concentrations and TTP. The prospective LIFE study measured several PFAS and metabolites in preconception serum; the only one associated with TTP was perfluorooctane sulphonamine (PFOSA) (FOR = 0.82 (0.71, 0.95)), although only 10% of samples had detectable levels (Buck Louis *et al.*, 2013). A subsequent reanalysis of the same data that adjusted for cycle length found reduced odds of conception among those in the highest versus lowest tertile of PFNA exposure while controlling for six other PFAS (OR = 0.7 (0.3, 1.1)) (Lum *et al.*, 2017). The retrospective Maternal-Infant Research on Environmental Chemicals (MIREC) study is a Canadian population-based study of women recruited in early pregnancy, at which time they provided plasma samples for measurement of PFOA, PFOS and PFHxS concentrations (Velez *et al.*, 2015). In results that combined parous and nulliparous women and did not adjust for parity, all three PFAS were associated with reduced fecundability (FOR = 0.89 (0.83, 0.94), 0.96 (0.91, 1.02) and 0.91 (0.86, 0.97), respectively) and higher odds of TTP >12 months (OR = 1.31 (1.11, 1.53), 1.14 (0.98, 1.34) and 1.27 (1.09, 1.48), respectively). This study was ranked 'good' on the NOS/AHRQ scale and met three additional quality metrics.

Finally, Ding *et al.* conducted a reanalysis of the PFAS data in the MoBA Study to account for the case-cohort sampling design, which had not been accounted for in the earlier analyses (Whitworth *et al.*, 2012, 2016). This failure time model analysis found a significant association of PFOA with longer TTP; however, the sample included both nulliparous and parous women (Ding *et al.*, 2014). The earlier Whitworth paper similarly found a link between PFOA and greater odds of infertility, but the association only persisted in parous women following stratification.

Evidence for shorter TTP

While no associations with TTP among nulliparous women were found when PFAS were modelled categorically in the large multisite European INUENDO study that recruited pregnant women and their male partners at their first prenatal visit from hospitals and antenatal clinics throughout Greenland, in Warsaw, Poland and in Kharkiv, Ukraine, an association between PFOA and shorter TTP among nulliparous women was reported when the exposure was modelled continuously. In the Ukrainian subsample, a 10-fold increase in PFOA was associated with a 46% increase in fecundability (2%, 108%), and when participants from Greenland, Poland and Ukraine were combined, a 31% increase in fecundability was observed (3%, 68%) (Jorgensen *et al.*, 2014).

Weight of evidence

Consistent null results from several high-quality studies that restricted their analyses to nulliparous women argue against any associations between PFAS and TTP. By contrast, two good studies did report associations of PFOS with longer TTP among nulliparous women, suggesting that the many members of the PFAS chemical class may not always act in concert. All but one of these studies used retrospective reports of TTP and measured PFAS in prenatal blood samples, yet the INUENDO study was the only one to adjust for gestational age at sampling even though PFAS levels are known to decline across pregnancy. Interestingly, the later of the two DNBC analyses reported discordant results between nulliparous and parous participants even though the authors adjusted for inter-pregnancy interval in the parous group, which theoretically should account for the gradual postnatal increase in PFAS following the decline during pregnancy and breastfeeding (Bach *et al.*, 2018). This suggests that the issue of bias in PFAS analyses conducted among parous or combined parous/nulliparous study populations may not be easily resolved. Further research is needed to explore more of the hundreds of PFAS in production that are not included in these analyses and determine whether they fall into groups that share common biological mechanisms and may have similar associations with reproductive outcomes such as TTP.

Associations of male exposures with TTP

Only four studies examined male exposure to POPs and TTP, yielding too little evidence to draw conclusions. Results were not always consistent with those found in female partners, suggesting that POPs may have sex-specific effects on gametogenesis, an avenue for future research.

OC pesticides

Evidence supporting an association between exposure to OC pesticides and TTP is slim. In a study of an historic cohort of 1223 men who lived in Sardinia during the anti-malarial campaign between November 1946 and May 1950, exposure to DDT was examined in relation to TTP, measured as the time lag between the date of marriage and the ninth month before the birth date of the first child (Campagna *et al.*, 2015). There was no statistically significant difference in fecundability between those exposed to DDT indirectly as bystanders (warehouse workers, drivers or inspectors in the campaign) or directly as pesticide applicators and those exposed at the background level in covariate-unadjusted analysis. Results were the same when DDT exposure was estimated based on the exact dates of starting

and ending each job, the task performed and the concentration of DDT in the insecticide preparation. This study ranked 'poor' on the NOS/AHRQ scale and met none of the additional quality metrics. There was also no association between preconception occupational exposure to any pesticides and retrospectively-assessed TTP among 2728 male participants in the Generation R Study (Snijder *et al.*, 2011).

By contrast, among 501 male participants in the prospective LIFE study, preconception exposure to p,p′-DDE measured in blood was associated with longer TTP (FOR = 0.83 (0.70, 0.97) in a covariate-adjusted model, although results were null for the other eight OC pesticides measured (Buck Louis *et al.*, 2013).

Brominated flame retardants

In keeping with results for female participants, there were no associations between male preconception PBB 153 or PBDE exposure and prospectively measured TTP in the LIFE study (Buck Louis *et al.*, 2013) or between male occupational exposure to flame retardants and retrospective TTP in the Generation R Study (Snijder *et al.*, 2011).

Polychlorinated organic compounds

As with female participants, the Generation R Study reported no association between male estimated occupational PCB exposure and TTP (Snijder *et al.*, 2011).

In the high-quality LIFE study, considerably more PCB congeners measured in male preconception serum were associated with longer TTP than in their female partners (PCBs 138, 156, 157, 167, 170, 172, 180 and 209). Several of these chemicals were detectable in <50% of samples, including PCBs 167 and 209, the only two with statistically significant results for both men and women. By contrast, PCB 101 was associated with shorter TTP (FOR = 1.28 (1.09, 1.51)), although it was detectable in only 38% of samples among males (Buck Louis *et al.*, 2013). Two reanalyses of the LIFE Study data examined joint associations of male and female partners' PCB exposure with risk of infertility (defined as TTP >12 months). Zhang *et al.* (2019) and Hwang *et al.* (2019) used different methods to examine joint exposure, but both found that summary measures of PCB exposure in both male and female partners were associated with couple infertility, with the male partners' PCB concentrations contributing more to infertility risk than the female partners'.

Per- and PFAS

The prospective LIFE study measured seven PFAS and metabolites in 501 male partners and found no association between any of them and TTP in an analysis that combined parous and nulliparous couples (Buck Louis *et al.*, 2013). The retrospective INUENDO study investigated 401 male partners' exposure, also combining parous and nulliparous couples, and found no association between PFOA, PFOS, PFHxS or PFNA with TTP when comparing those in the highest tertiles of exposure to the lowest. When male PFAS concentrations were modelled continuously, however, a 10-fold increase in PFNA among Greenland participants was associated with a 30% decrease in fecundability (1%, 50%); there were no associations for other PFAS or for men from Poland or Ukraine (Jorgensen *et al.*, 2014).

Discussion

The relationship between specific POPs and fecundability has been studied in a variety of settings; however, we are not aware of any prior systematic reviews that summarise across chemical classes. After conducting our exhaustive review of five major databases for English-language empirical studies published in the past 12 years, the combined evidence suggests that at least some of these chemicals may have negative effects on reproductive processes that contribute to delayed TTP (Table VI). Of note, our review lends support for adverse effects of female exposure to PCBs on fecundability, with some additional support for associations of female exposure to PBDEs and select PFAS with longer TTP. In contrast, the systematic review provided little or no support for associations between female exposure to OC pesticides and TTP. There were too few studies of male exposure to any of the POP groups and fecundability to draw conclusions, although there was suggestive evidence of a link between male PCB exposure and TTP in one high-quality prospective study.

In addition to being an indicator of subfecundity that may warrant medical intervention such as IVF, delayed TTP is of public health importance because it may be a predictor of future health problems for both men and women. Men with poor semen quality, a contributing factor to couple subfecundity, are at elevated risk of non-reproductive cancers (Ku *et al.*, 2015), cardiovascular disease (Eisenberg *et al.*, 2015), diabetes (La Vignera *et al.*, 2012), autoimmunity (Glazer *et al.*, 2018; Brubaker *et al.*, 2018), overall morbidity (Salonia *et al.*, 2009;

Table VI Summary of the weight of evidence among papers reviewed on female exposures[1] to persistent organic pollutants and fecundability.

			No association with TTP	Associated with longer TTP
Strength of evidence	*High*	*Polychlorinated biphenyls (PCBs)*[2]		√
		Organochlorine (OC) pesticides	√	
		Per- and polyfluoroalkyl substances (PFAS)[3]	√	
	Low	*Brominated flame retardants (BFRs)*		√

[1]There was too little evidence to draw conclusions for male exposures.
[2]While most PCBs were associated with longer TTP, certain congeners were associated with shorter TTP.
[3]Evidence was strongest among studies that were restricted to nulliparous women.

Eisenberg et al., 2015; Latif et al., 2017) and mortality (Groos et al., 2006; Jensen et al., 2009; Eisenberg et al., 2014). Women with conditions that contribute to infecundity such as polycystic ovarian syndrome (de Groot et al., 2011; Lim et al., 2019; Ramezani Tehrani et al., 2020), endometriosis (Tan et al., 2019) and premature ovarian failure (Muka et al., 2016; Honigberg et al., 2019; Zhu et al., 2019) as well as women who experience failed fertility therapy (Udell et al., 2017) are at increased risk of metabolic syndrome, cardiovascular disease, adverse birth outcomes and overall mortality. These associations likely are not causal, but result from common causes, which may include exposure to POPs.

Study limitations

While we found heterogeneity in the quality of the studies we reviewed on POPs and TTP, most ranked highly, with 11 out of 19 receiving a 'good' NOS/AHRQ rating and meeting 3 or 4 additional quality metrics. Nevertheless, all neglected to adjust for multiple comparisons, increasing the likelihood of Type I error (i.e. that a significant effect was erroneously reported), especially in analyses that examined chemicals from different classes, which are less likely to be highly correlated. Selection bias is of concern for retrospective studies, as they condition on both conception and continued pregnancy either until the time when biospecimens are collected or live birth in cases when exposure is measured in cord blood, when pregnancy duration/live birth may be associated with both the chemical being studied and TTP. Exposure measured in a spot blood sample may be a source of measurement error, as it may not represent exposure at the time of conception for POPs with short half-lives (e.g. BDE 209, which has a half-life of about 2 weeks).

Across studies, statistical models adjusted for different sets of covariates; while this may be due to varying sources of confounding in different populations (e.g. socioeconomic status may be related to POP exposure in some populations but not others), in some cases this was due to a lack of agreement on appropriate confounders. The INUENDO study was the only retrospective PFAS study to include gestational age at blood sampling, which is appropriate as concentrations decline across pregnancy. A recent study by Buck Louis et al. (2019) suggests that concentrations of other POPs may also vary across pregnancy, indicating that adjusting for gestational age at sampling may be good practice for all of these chemical classes.

Several PFAS studies combined parous and nulliparous women in their analyses, even though PFAS levels have been shown to decline with increasing parity, likely because women transfer PFAS to their foetuses/offspring during gestation and breastfeeding. Other POPs have also been shown to decrease with parity (Fisher et al., 2016), raising the question of whether all analyses of POPs and TTP should be conducted in nulliparous women. Because pregnancy involves the mobilisation and remodelling of adipose tissue and that redistribution may differ by overweight/obesity status (Straughen et al., 2013), BMI and gestational weight gain may affect prenatal blood concentrations of lipophilic POPs in retrospective studies.

Comparisons of results across studies were complicated, as studies measured different chemicals and congeners. While chemicals from the same class were generally measured similarly (e.g. gas chromatography-mass spectrometry for PCBs, PBBs, PBDEs and OCs; liquid chromatography-mass spectrometry for PFAS), details of the procedures varied by laboratory. The issue of whether these differences substantially impact results is directly addressed by Sholtz et al. (2011), who found that measurements of chlorinated pesticides and PCBs were able to be combined over a 13-year period without meaningful misclassification due to laboratory variation or time period. Moreover, exposures were modelled differently across the studies we reviewed, with some studies choosing to log-transform their data and/or categorise exposures using sample-specific cut-points, including the LOD, which also varied by laboratory. Each study population had a different exposure distribution, frequently dependent on both geography and time period. Finally, study populations were likely exposed to different mixtures of chemicals, and interactions among them may distort results when chemicals' associations with TTP are assessed individually.

Future research

The results of this systematic review indicate several recommendations for future research. First, although prospective fecundability studies using daily pregnancy tests are expensive and logistically difficult and may not be generalisable to the broader population as they are restricted to pregnancy planners, they are optimal for accurate exposure and outcome assessment. Prospective studies measure the exposure prior to the outcome, strengthening the evidence for causation, and avoid both inaccuracies in outcome measurement due to recalled TTP and selection bias based on conception, pregnancy continuation or live birth. Second, when studying POPs with short half-lives, the body burden may be better captured with repeated biosamples across the preconception period, mitigating exposure misclassification. Third, in order to ensure that models include appropriate covariates (e.g. pre-pregnancy BMI) and results are analysed in appropriate subsamples (e.g. nulliparous women), further exploration of the metabolism and toxicokinetics of these chemicals is necessary, particularly during pregnancy. Fourth, studies need to consider POPs that are less commonly studied and those that are replacing chemicals that are being voluntarily phased out, regulated or banned, including new generations of BFRs and PFAS (Pellizzari et al., 2019).

With respect to data analysis, attention should be paid to distributions of chemicals, as variations across populations may complicate cross-study comparisons. Chemical mixtures analyses and analyses considering interactions between chemical exposures and non-chemical exposures (e.g. psychosocial measures, genotypes, diet and activity) are important to consider, although samples need to be large in order to achieve adequate statistical power. As a result, prospective multi-site studies that are designed so that pooled analyses may be conducted are ideal to clarify the complex effects of these chemicals on fecundability. Such studies would preclude difficulties caused by cross-study comparisons of studies using different confounders, means of exposure and outcome assessment and exposure distributions, and ensure adequate power to test for interactions.

Conclusions

While results were not consistent among the 28 articles from 19 different studies that we reviewed, at least some POPs appear to be associated with reduced fecundability. The evidence was strongest for

female exposure to PCBs and weakest for OC pesticides, with equivocal findings for PBDEs and PFAS. Results for male exposure were limited and inconclusive. In terms of BFRs and PFAS in particular, more research needs to be done, as there are numerous members of these chemical classes that have not been studied in relation to TTP, including newer 'replacement' molecules that are being introduced as studies have shown adverse health outcomes associated with older ones. 'Legacy' chemicals such as DDT and PCBs, which have been regulated or banned in most parts of the world, still merit attention, as their persistence in the environment and the human body means that they will continue to affect human health for years to come. These health effects are not evenly distributed across populations, with countries in the Global South bearing a higher burden, as OC pesticides may still be used to combat tropical disease and industries such as e-waste recycling expose workers to PCBs, dioxins and furans, which also contaminate soil and groundwater (Chakraborty *et al.*, 2018). Even within developed countries, risk is not equally shared, as disadvantaged communities are more likely to live near industrial and military sites that have contaminated the surrounding environment. In addition, individuals with lower income are less able to afford to replace older furniture and household goods that may contain PBDEs and PFAS. To the degree that these populations are at elevated risk of exposure, they may also be at risk for decreased fecundability, impacting not only their ability to reproduce, but also indicating increased likelihood of long-term health problems. Additional research is needed to understand how associations between POPs and TTP may vary by population, how POPs may interact with other chemical and non-chemical exposures, and how POPs are distributed in and metabolised by the human body, especially during the periconceptional and prenatal periods. The results of such studies should be summarised and disseminated to clinicians, who can then inform patients about the potential for POPs to interfere with reproductive function and provide advice about ways to reduce exposure.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Authors' roles

Study conception and design: L.G.K., K.G.H., E.L.S., P.F.-L., C.A.P. and A.E.H.; search strategy design and execution: M.K.-F.; data extraction and interpretation: L.G.K., K.G.H., E.L.S., Y.Z., P.F.-L., C.A.P. and A.E.H.; drafting, critical revision and final approval of the manuscript: all authors.

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Conflict of interest

None declared.

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