

Science linking environmental contaminant exposures with fertility and reproductive health impacts in the adult female

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Study Objective: To broadly review the recent literature linking environmental factors and adult female reproductive health for the UCSF–CHE Summit on Environmental Challenges to Reproductive Health and Fertility.

Design: Reviewed articles indexed in PubMed from 1999–2007 addressing environment and puberty, menstrual and ovarian function, fertility, and menopause.

Result(s): The strongest evidence of environmental contaminant exposures interfering with healthy reproductive function in adult females is for heavy metals, particularly lead. Compounds that can influence hormone function, including pesticides and persistent pollutants, are also associated with risk. The pattern of effects for these endocrine-active compounds is often complex, with no clear dose response, but alterations in function and poor reproductive health outcomes are observed. From a clinical perspective, most modifiable risk appears to be associated with exposures in unique populations (contaminated fish consumers) or occupational groups (farmworkers). Many compounds have demonstrated increased risks for reproductive health impairment in women, but the literature is largely cross-sectional in nature and too sparse or inconclusive to support causal inference.

Conclusion(s): Reproductive function in adult females is impaired by lead exposure. Pesticides and persistent pollutants can alter hormone function resulting in adverse reproductive health effects. Coordinated research is needed to address contaminant effects across the life span. (Fertil Steril® 2008;89:e81–94. ©2008 by American Society for Reproductive Medicine.)

Key Words: Review, female, reproductive health, environmental contaminants, puberty, menstrual function, ovarian function, fertility, fecundity, time-to-pregnancy, menopause

Considerable public concern exists regarding the role environmental contaminants play in human health. Here we review the biomedical literature for human data and key animal studies linking environmental contaminant exposures and reproductive health in adult females in preparation for the University of California at San Francisco–Collaborative on Health and the Environment (UCSF–CHE) Summit on Environmental Challenges to Reproductive Health and Fertility, held in January 2007. As part of a series of overview presentations, this review is focused on postnatal exposures and outcomes in adult women and girls approaching puberty. Developmental effects and most pregnancy outcomes (except spontaneous abortion) are covered elsewhere in these proceedings.

MATERIALS AND METHODS

We examined review articles and original research reports from 1999 to 2007 indexed in PubMed using the following

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search terms: environmental, environmental contamination, environmental pollution, environmental tobacco smoke, second hand smoke; puberty, precocious puberty, delayed puberty, menarche timing, breast development, hair growth; menstrual and ovarian function, menstruation, ovarian function, menstrual regularity, menstrual dysfunction, endometriosis, fibroids, polycystic ovary syndrome; fertility and fecundity, subfertility, time to pregnancy, spontaneous abortion, infertility; menopause, and reproductive senescence. All articles reporting human data were reviewed, and key animal studies were evaluated to illustrate emerging directions in research or elucidate biologic plausibility and mode of action. The review and the results were organized by life stage because each stage of reproductive health (puberty, menstrual and ovarian function, fertility and fecundity, menopause) is dependent upon achieving a functional level of biologic competence in previous stages.

RESULTS

Puberty

Puberty is an outcome occurring over several years, with breast and pubic hair development serving as indicators of pubertal progress. Stages of development can be measured by clinicians, and have been based on self-report in some research efforts. Menarche, or the initiation of menstruation, is

a key pubertal milestone frequently considered in environmental epidemiologic research.

Environmental contaminants can both accelerate or delay pubertal development. Lead exposure appears to delay puberty in girls, even at very low levels (<5 µg/dcl) (Table

1). Studies based on the National Health and Nutrition Examination Survey III, a representative cross-section of American girls, found delays in menarche and other pubertal markers (1, 2). Later menarche was also associated with lead exposure in a study of 138 Native American girls from upstate New York (3).

TABLE 1

Environmental contaminants (heavy metals, persistent organic pollutants, other) and puberty outcomes from the biomedical literature, 1999–2007.

	Author (Reference)	Exposure	Outcome	Findings
Metals	Selevan et al., 2003 (2)	Serum lead	Menarche attainment Breast development Pubic hair stage	Delayed menarche (AA, MA) Delayed breast (AA, MA) Delayed public hair (AA, MA)
	Wu et al., 2003 (1)	Serum lead	Menarche attainment Breast development Public hair stage	Delayed menarche No association Delayed pubic hair stage
Persistent Pollutants	Denham et al., 2005 (3)	Serum lead Serum PCB	Menarche attainment	Nonlinear delayed menarche Increased risk of menarche No association
	Krstevska-Konstantinova et al., 2001 (6)	Serum DDE, Mirex, HCB Serum p,p'-DDE	Precocious puberty	Increased risk for foreign-adopted girls compared with foreign not-adopted girls
	Den Hond et al., 2002 (7)	Serum PCB (138, 153, 180)	Menarche attainment Breast development Pubic hair stage Menarche onset	No association Less breast development No association No association
	Warner et al., 2004 (9) Ouyang et al., 2006 (5) Axmon et al., 2006 (8)	Serum TCDD Serum DDT Living in Baltic fishing village	Age at menarche Age at menarche	Younger age at menarche Older age at menarche
Other	Colon et al., 2000 (4)	Serum DOP Serum DEHP Serum MEHP DBP, DEP, BBP	Premature thelarche	Increased risk Increased risk No detectable blood levels

Note: AA = African American; DBP = dibutyl phthalate; DDE, p,p'-DDE = dichlorodiphenyldichloroethylene; DDT = 1, 1-bis-(4 chlorophenyl)-2,2,2-trichloroethane; DEHP = di-2-ethyl hexyl phthalate; DEP = diethyl phthalate; BBP = benzyl butyl phthalate; DOP = dioctyl phthalate; HCB = hexachlorobenzene; MA = Mexican American; MEHP = mono-ethyl-hexyl phthalate; PCB = polychlorinated biphenyls; TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxin.

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TABLE 2

Environmental contaminants (heavy metals, pesticides, persistent organic pollutants, other) and menstrual outcomes from the biomedical literature, 1999–2007.

	Author (Reference)	Exposure	Outcome	Findings
Metals	Tang and Zhu, 2003 (10)	Lead battery plant workers	Polymenorrhea, long menstruation, hypermenorrhea	Increased odds
	Yang et al., 2002 (90)	Workers in lamp factory (mercury)	Dysmenorrhea	Increased odds
	Wang and Tian, 2004 (16)	Lead–zinc mine, cadmium	Menstrual abnormalities	No effect
Pesticides	Farr et al., 2004 (13)	Lifetime pesticide use	Long cycles Missed periods Irregular cycles	Increased odds Increased odds Decreased odds
		Lindane, Atrazine Mancozeb, Maneb	Intermenstrual bleeding	Increased odds Increased odds
Persistent Organic Pollutants	Ouyang et al., 2006 (5)	Serum DDT	Short cycle	Increased odds
	Perry et al., 2006 (20)	Serum DDT	Estrogen conjugate (E1C)	Decreased E1C in periovulatory phase
			Pregnanediol-3-glucuronide (PdG)	Decreased PdG in luteal phase
	Chen, et al., 2005 (18)	Serum DDT, DDE	Cycle length, duration, flow	No effect
	Windham, et al., 2005 (21)	Serum DDT, DDE	Luteal phase	Shorter luteal phase
			Progesterone metabolite	Less progesterone metabolite
	Cooper et al., 2005 (14)	Serum PCB	Cycle characteristics	No effect
			Cycle length Irregular cycles	Longer cycles Irregular cycles (highest exposure) No effect
Gerhard et al., 1999 (19)	Serum PCB	Duration, flow, dysmenorrheal	No effect	
		FSH levels LH levels DHEAS levels DHEA levels	Lower FSH Lower LH Lower basal DHEAS Lower basal DHEA	
Yu et al., 2000 (17)	PCB tainted oil	Abnormal bleeding Other menstrual characteristics	Increased risk No effect	

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TABLE 2

Continued.

	Author (Reference)	Exposure	Outcome	Findings
	Eskenazi et al., 2002 (12)	Serum TCDD	Cycle length	If premenstrual exposure, longer cycles
Other	Hsieh et al., 2005 (15)	Photolithography (EGE, IPA)	Cycle length	Longer cycles
		Diffusion (HFA, IPA, P)	Cycle length	Longer cycles
	Windham et al., 2003 (11)	TTHM levels	Cycle length Follicular length	Decreased cycle length Decreased follicular length

Note: DDT = 1,1-bis-(4 chlorophenyl)-2,2,2-trichloroethane; DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate; EGE = ethylene glycol ethers; FSH = follicle stimulating hormone; HFA = hydrofluoric acid; IPA = isopropyl alcohol; LH = lutenizing hormone; P = phosphorous; TTHM = total trihalomethanes; PCB = polychlorinated biphenyls; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

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Earlier age at puberty, including outcomes such as thelarche and precocious puberty, as well as earlier age at menarche have been observed with exposure to phthalates (4), serum dichlorodiphenyl trichloroethane (DDT) (5), and its primary metabolite 1,1,-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (DDE) (6), and polychlorinated biphenyls (PCBs) (3).

Delays in some pubertal markers have been seen in other studies of persistent pollutants. Exposure to tetrachlorodibenzo-*p*-dioxin (TCDD) (7) was associated with delayed breast development, and slight delays in age at menarche were observed among consumers of contaminated Baltic Sea fish (8). However, age at menarche was not related to dioxin exposure in the den Hond study (7), and no effect on menarchal age was observed among girls exposed to dioxin prepuberty in Seveso (9). Serum DDE and mirex were not related to menarche in the study by Denham et al. (3).

In general, lead appears to be associated with pubertal delay but the evidence for persistent pollutants is less clear. Most investigations show an association with accelerated puberty, but the magnitude of the effects is inconsistent, and findings do not support a dose–response relationship.

Menstrual and Ovarian Function

Variations in menstrual and ovarian function have been observed following consumption of drinking water disinfection byproducts (DBPs) and fish contaminated with PCBs and other pollutants; similar associations were noted in studies using biologic markers of TCDD, DDT, DDE, and PCBs. These studies generally describe functional variations (long or short cycles, changes in luteal or follicular phase) that in-

dicate an underlying perturbation of hormones rather than the development of clinical disorders.

Shorter cycles have been observed among lead-battery plant workers (10) as well as women exposed to chlordibromomethane in drinking water (11) and DDT (5) (Table 2). Longer cycles have been observed in other studies of endocrine-active compounds such as TCDD (12), hormonally active pesticides (13), serum PCBs (14), and working in the semiconductor industry with exposure to a variety of chemicals such as ethylene glycol ethers (15). Some of these studies also found evidence of menstrual disorders (10, 13, 14) such as missed periods and abnormal bleeding. Other studies found menstrual abnormalities associated with PCBs or metal exposure with no change in cycle length (16, 17). One study found no association with menstrual cycle characteristics and serum DDE or DDT among 47 Chinese women (18).

Follicle-stimulating hormone was decreased in women exposed to pentachlorophenol (19). Progesterone and estrogens have been reduced in women exposed to DDT and DDE (20, 21), but no differences were observed in hormone profiles related to PCB level (20, 21).

Endometriosis, the presence of functional endometrial tissue outside of the uterine lining, has been widely studied. Most of the work addressing TCDD (dioxins) exposure found no difference in serum dioxin levels between women with and without endometriosis (Table 3). Many of these studies have been limited to specific populations [infertile women (22) or uniquely exposed populations (12)]. Most of the studies considering PCBs, however, found increased serum PCB values among endometriosis cases, compared with controls.

TABLE 3**Environmental contaminants (heavy metals, persistent organic pollutants, other) and endometriosis from the biomedical literature, 1999–2007.**

	Author (Reference)	Exposure^a	Outcome	Findings
Metals	Heilier et al., 2004 (Belgium) (91)	Serum cadmium	Endometriosis	No effect
Persistent Organic Pollutants	Shi et al., 2006 (China) (92)	TCDD	Inflammation markers among endometriosis	Increased risk
	Yoshida et al., 2000 (Japan) (93)	TCDD	Cancer, reproductive endometriosis, infant neurobehavior	No effect
	Eskenazi et al., 2002a (USA) (94)	TCDD	Endometriosis	No effect
	Lim et al., 2004 (Korea) (95)	Food, milk, serum TCDD	Cancer, reproductive endometriosis, infant neurobehavior	No effect
	Pauwels et al., 2001 (Belgium) (22)	Dioxins, coplanar PCBs	Endometriosis	No association in infertile women
	Fierens et al., 2003 (Belgium) (23)	PCDD, PCDF, coplanar PCB	Endometriosis	No effect
	De Felip et al., 2004 (Italy) (96)	PCDD, PCDF, dioxin-like PCB	Endometriosis	No effect
	Quaranta et al., 2006 (Italy) (97)	PCBs, p,p'-DDE	Endometriosis; immune parameters among cases	Increased risk
	Rier 1999 (USA) (98)	TCDD (TEQs), PCB 77, 126	Endometriosis	Increased risk, severity; immune alterations
	Porpora et al., 2006 (Italy) (99)	PCBs	Endometriosis	Increased risk
	Heilier et al., 2004 (Belgium) (100)	PCB	Rectovaginal adenomyosis	Increased risk (no effect for endometriosis)
	Buck Louis et al., 2005 (USA) (101)	PCB congeners	Endometriosis	Increased risk (antiestrogenic PCBs)
	Gerhard et al., 1999 (Germany) (102)	Chlorinated hydrocarbons	Endometriosis	Increased risk for PCBs in infertile women
Reddy et al., 2006 (India) (103)	PCBs, PEs	Endometriosis	Increased risk	

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TABLE 3

Continued.

	Author (Reference)	Exposure ^a	Outcome	Findings
Other	Reddy et al., 2006a (India) (25)	Phthalate esters	Endometriosis	Increased risk
	Cobellis et al., 2003 (Italy) (24)	DEHP, MEHP	Endometriosis	Increased risk for DEHP
	Taskinen et al., 1999 (Finland) (74)	Formaldehyde, organic solvents	Endometriosis	Increased risk
	Carpenter et al., 2001 (USA) (104)	Residence in one of three NY state's Areas of Concern	Endometriosis	Increased risk

Note: DDE, p,p'-DDE = dichlorodiphenyldichloroethylene; DEHP = Di-(2-ethylhexyl)-phthalate; MEHP = Mono-ethylhexyl phthalate; NY = New York; PCB = polychlorinated biphenyls; PCDD = polychlorinated dibenzodioxins; PCDF = polychlorinated dibenzofurans; PE = phthalate esters; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TEQs = toxic equivalence.

^a Serum or plasma levels, unless otherwise noted.

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A very small study of 10 endometriosis cases and 132 controls found no association with PCBs (23). Phthalate esters have also been associated with endometriosis among some women (24, 25).

Most of the literature on fibroids (26) and polycystic ovarian syndrome (27) implicates developmental exposures. In addition to developmental effects (28), there appears to be a role for persistent endocrine-active pollutants in the risk for endometriosis among adults. The evidence addressing adult contaminant exposure effects on polycystic ovarian syndrome or fibroids is too sparse to evaluate meaningful effects.

Fertility and Fecundity

A large amount of the literature devoted to adult female reproductive health effects is focused on the area of fertility and fecundity. Fertility and fecundity studies include time to pregnancy and spontaneous abortion outcomes, as well as studies of infecundity and other measures of subfertility (Table 4). As noted in previous sections, lead appears to be a consistent reproductive toxicant (10, 29). There are two recent reports that do not find associations with lead or presumed lead exposure (30, 31), but one compares blood lead results from 20 women who experienced a pregnancy loss with the blood lead levels of 20 pregnant women (30). This comparison is troublesome because metals will be released from bone during pregnancy, and despite the author's claim, it is unlikely they can control for this physiologic difference in their data. The second is a population-based study of women living near a smelter that fails to replicate associations with spontaneous abortion observed in the 1970s, and the authors presume the increased reproductive health is a result of lower emissions over time (31).

Exposure to most persistent organochlorines appears to increase risk in several studies, but the results are inconsistent, especially for PCBs. PCB-contaminated fish consumption from the Baltic Sea had no impact on fertility (32–34), except in a subgroup analysis of heavy smokers; studies of serum PCB measures in the same populations also observed no effect (35, 36). In contrast, effects were observed in association with Great Lakes fish consumption (37, 38) although the results were generally weak, and in one study vanished after adjusting for male partner fish consumption (39). No effect in association with exposure to PCB-contaminated cooking oil was observed (17), but there was a suggestion of increased time to pregnancy related to increased PCBs and DDE in serum from the Collaborative Perinatal Project (40). Toft and colleagues found regional variations in fertility that could be explained by population differences in DDE levels, but saw no relation to an indicator PCB (PCB-153) (41). Recurrent pregnancy loss was not associated with hexachlorobenzene, DDE, or PCB levels (42). Spontaneous abortion risk was not associated with TCDD exposure in Seveso (43), but was found to be associated with living in petroleum hydrocarbon-contaminated areas in Ecuador (44). In a very small study, DDE was nearly doubled in 15 Chinese textile workers who had spontaneous abortions compared with 15 women with full-term births (45). Early pregnancy losses identified by biomonitoring were associated with serum DDT and metabolites, but no association was observed for clinical losses (46). Increased risk for a prior spontaneous abortion was observed when serum DDT and DDE levels were measured in late pregnancy, but no clear dose response was found (47).

Working with or applying pesticides, primarily in agricultural and horticultural settings, appears to consistently reduce

TABLE 4**Environmental contaminants (heavy metals, pesticides, persistent organic pollutants, other) and fecundity and fertility outcomes from the biomedical literature, 1999–2007.**

	Author (Reference)	Exposure	Outcome	Risk
Metals	Chang et al., 2006 (29)	Lead, blood	Infertility	Increased
	Wang and Tian, 2004 (16)	Cadmium, soil and water samples, interview	Difficulty becoming pregnant	Increased
	Tang and Zhu, 2003 (10)	Lead, interview	SAB	Increased
	Faikoglu et al., 2006 (30)	Lead, blood	Early pregnancy loss	No effect
	Wulff et al., 2002 (31)	Living near a smelter, interview	SAB	No effect
Pesticides	Greenlee et al., 2003 (52)	Herbicide and fungicide use/application	Infertility	Weak
	Curtis et al., 1999 (50)	Pesticides, farming, interview	TTP	Increased
	Abell et al., 2000 (48)	Pesticides, greenhouse work, interview	TTP	Increased
	Idrovo et al., 2005 (53)	Pesticides, flower production, interview	TTP	Increased
	Lauria et al., 2006 (54)	Pesticides, greenhouse work, interview	TTP	No effect
	Arbuckle et al., 1999 (56)	Pesticides, farm, interview	SAB	Increased
	Arbuckle et al., 2001 (59)	Pesticides, farm, interview	SAB	Increased
	Crisostomo et al., 2002 (49)	Pesticides, farm, interview	SAB	Increased
	Garry et al., 2002 (51)	Personal use of pesticides, interview	Pregnancy loss	Increased
	Bindali et al., 2002 (57)	Pesticides, mancozeb, mice	Inhibition of implantation	Increased
	Greenlee et al., 2004 (58)	Pesticides, mice	Developmental toxicity in preimplantation embryos	Increased

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TABLE 4

Continued.				
	Author (Reference)	Exposure	Outcome	Risk
Persistent Organic Pollutants	Axmon et al., 2000 (33)	Living in Baltic fishing village, interview	Miscarriage	No effect
	Axmon et al., 2000 (32)	Living in Baltic fishing village, interview	TTP, Infertility	Increased (heavy smokers only)
	Axmon et al., 2002 (34)	Living in Baltic fishing village, interview	TTP, Subfertility, Miscarriage	No effect
	Axmon et al., 2001 (35)	PCB biomarker, serum	TTP	No effect
	Axmon et al., 2004 (36)	PCBs, serum	TTP	Decreased
	Buck et al., 2000 (37)	Years of fish consumption, interview	TTP, Reduced fecundability	Increased
	Courval et al., 1999 (39)	Lifetime sport-fish consumption, interview	Conception delay	No effect
	McGuinness et al., 2001 (38)	Consumption of Great Lakes caught fish, interview	Resolved and unresolved fecundity (TTP)	Weak
	Yu et al., 2000 (17)	PCB contaminated cooking oil, serum	Longer than 1 year to become pregnant, diagnosed fertility problem, SAB	No effect
	Law et al., 2005 (40)	PCBs and DDE, serum	TTP	Weak
	Toft et al., 2005 (41)	DDE, PCB (CB-153), serum	TTP	Increased (DDE)
	Venners et al., 2005 (46)	DDT, serum	Miscarriage	Increased
	Korrick et al., 2001 (45)	DDE, serum	SAB	Increased
	Sugiura-Ogasawara et al., 2003 (42)	DDE, PCBs, serum	Recurrent miscarriage	No effect
	Longnecker et al., 2005 (47)	DDE, serum	Previous fetal Loss	Increased
	Eskenazi et al., 2003 (43)	TCDD, serum	SAB	No effect
Gerhard et al., 1999 (102)	Chlorinated hydrocarbons, serum	Infertility, miscarriage	Increased	

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TABLE 4

Continued.

	Author (Reference)	Exposure	Outcome	Risk
	San Sebastian et al., 2002 (44)	Living in petroleum hydrocarbon-polluted areas, water data, interview	SAB, last three pregnancies	Increased
Other	Sallmen et al., 2006 (71)	Solvents, interview	Subfertility	Increased
	Doyle et al., 2001 (64)	Ionizing radiation, monitors	Primary Infertility	Weak
	Mohallem et al., 2005 (68)	PM10 and NO ₂ , mice	Number of live pups, implantation failure	Increased
	Chen et al., 2002 (62)	Semiconductor industry, ethylene glycol ethers, interview	TTP	Increased
	Dejmek et al., 2000 (63)	SO ₂ , air data, likely male mediated	TTP	Increased
	Hull et al., 2000 (66)	Active and passive smoking, interview	Delayed conception	Increased
	Neal et al., 2005 (69)	Sidestream smoking, interview— IVF population	Implantation rate, pregnancy rate	Decreased
	Wennborg et al., 2001 (75)	Laboratory work with solvents, interview	TTP	Increased
	Plenge-Bonig et al., 1999 (70)	Printing industry, toluene, interview	Subfecundity, TTP, PUNP	Increased
	Taskinen et al., 1999 (74)	Wood workers, formaldehyde, interview	Delayed conception, SAB	Increased
	Axmon et al., 2006 (60)	hairdressing work, interview	TTP	Increased
	Bielmeier et al., 2001 (61)	Disinfection byproduct BDCM, rat	Full litter reabsorption	Increased
	Savitz et al., 2006 (72)	Disinfection byproducts, water data	Pregnancy loss	Weak
	Sugiura-Ogasawara et al., 2005 (73)	Bisphenol-A, blood	Recurrent miscarriage	Increased
	Elliott et al., 1999 (65)	Semiconductor industry, interview	SAB	No effect

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TABLE 4

Continued.

Author (Reference)	Exposure	Outcome	Risk
Windham et al., 1999 (76)	ETS, interview	SAB	No effect
Auvinen et al., 2001 (59)	Radioactivity (Chernobyl), spectrometer survey	SAB	Weak
Lee et al., 2002 (67)	Residential and personal magnetic fields, monitors	Clinical miscarriage	Increased

Note: SAB = spontaneous abortion; TTP = time to pregnancy; DDE, p,p'-DDE = dichlorodipenyldichloroethylene; DDT = 1,1-bis-(4 chlorophenyl)-2,2,2-trichloroethane; PCB = polychlorinated biphenyls; SAB = spontaneous abortion; TCDD = 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TTP = time to pregnancy; BDCM = bromodichloromethane; ETS = environmental tobacco smoke; IVF = In vitro fertilization; NO₂ = nitric dioxide; PM10 = particulate matter, 10 nanometers in diameter; PUNP = periods of unprotected intercourse not leading to pregnancy; SAB = spontaneous abortion; SO₂ = sulfur dioxide; TTP = time to pregnancy.

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fertility and/or fecundability (48–53), although this effect was not observed in the adjusted analysis of greenhouse workers in Italy (54). Preconception exposure appears to elevate risk for spontaneous abortion (55) but not exposure during pregnancy (56). Although animal studies during this time period were limited, pesticides have shown detriments in both fecundity and fertility (57, 58).

Additional environmental exposures, including bis-phenol A, solvents, radiation, and other compounds (59–76) have also been associated with decrements in female fertility, but the literature is limited or inconclusive. In particular, studies of solvent exposure in a variety of settings (70, 71, 75) suggest decreases in fertility.

Menopause

Menopause is the final life stage for which we evaluated environmental effects research. During this stage there are changes in hormone levels with decreases and/or irregularities in ovulation, menstrual cycling, and fecundity. These changes eventually lead to reproductive senescence when the ovaries produce only low amounts of progesterone and estrogen, eggs are no longer released, and menstruation ceases. Menopause has not been extensively studied, but earlier age at menopause has been observed with exposure to serum dioxin (77) (Table 5). Age at natural menopause was also younger for women exposed to DDT, DDE, and other pesticides in data from the Hispanic Health and Nutrition Examination Survey (78). Neither PCBs or polybrominated biphenols (PBBs) were associated with menopause in the Michigan PBB cohort study (79), and PCB-exposed women from the Taiwan Yucheng cohort did not experience differences in age at menopause compared with controls (17). Data from plasma samples deriving from a cancer case-control study suggest that DDE has a weak association with earlier age at

menopause but PCBs have no effect (80). Being a current smoker also appears to lower the age a menopause, whereas past or passive smoking does not (81). In contrast, DDT exposure in the Agricultural Health Study was associated with slightly older age at menopause (82). In animal studies that may help elucidate underlying mechanisms, follicle destruction was found to occur after exposures to mancozeb, dibromoacetic acid, polycyclic aromatic hydrocarbons, cyclophosphamide, and 4-vinylcyclohexene diepoxide (83–88). Lead disrupted folliculogenesis in a study in mice (89).

DISCUSSION

Limitations of Existing Research

The large number of studies represented in this time-limited review demonstrates the substantial interest, on the part of researchers and funding agencies, in environmental contamination and reproductive health. However, the existing literature is limited in several ways. Frequently, researchers conduct environmental studies in human populations using convenience samples. Studies often focus on a unique geographic area or specific groups of individuals (e.g., all women working at a specific industry). Second, environmental research on women's reproductive health generally makes use of existing data. Although it is important to make use of existing specimen sources, data collected for other research or clinical purposes will rarely include specific exposure timing or important confounder information. Third, the studies represented here are largely cross-sectional and retrospective. Using cross-sectional data means the most relevant exposure measurements are either not available for critical time windows or subject to recall by participants. The most critical issues in the field—specifically, how exposure timing, developmental effects, dosage, and susceptibility factors influence reproductive health—cannot be adequately addressed without longitudinal

TABLE 5**Environmental contaminants (heavy metals, pesticides, persistent organic pollutants, other) and menopause outcomes (including follicular destruction) from the biomedical literature, 1999–2007.**

	Author	Exposure	Outcome	Risk
Metals	Taupeau et al., 2001 (89)	Lead, mice	Follicle dysfunction	Increased
Pesticides	Baligar et al., 2001 (83)	Mancozeb, rats	Follicle destruction	Increased
	Farr et al., 2006 (82)	Pesticides, interview	Menopause	Decreased
Persistent Organic Pollutants	Akkina et al., 2004 (78)	DDT, pesticides, serum	Menopause	Increased
	Cooper et al., 2002 (80)	DDE and PCBs, serum	Menopause	Increased (DDE)
	Yu et al., 2000 (17)	PCB/PCDF, serum	Menopause	No effect
	Blanck et al., 2004 (79)	PCBs, PBB, serum	Menopause	No effect
	Eskenazi et al., 2005 (77)	Dioxin, serum	Menopause	Increased
Other	Bodensteiner et al., 2004 (84)	Dibromoacetic acid, rabbits	Follicle destruction	Increased
	Borman et al., 2000 (85)	PAH, rats, and mice	Follicle destruction	Increased
	Cooper et al., 1999 (81)	ETS, interview	Menopause	No effect
	Meirow et al., 1999 (88)	Cyclophosphamide, mice	Follicle destruction	Increased
	Huong et al., 2002 (105)	Chemotherapeutic agents	Menopause	Increased
	Kao et al., 1999 (86)	VCD, rats and mice	Follicle destruction	Increased
	Mayer et al., 2002 (87)	VCD, rats	Follicle destruction	Increased

Note: DDE, p,p'-DDE = dichlorodiphenyldichloroethylene; DDT = 1,1-bis-(4 chlorophenyl)-2,2,2-trichloroethane; ETS = environmental tobacco smoke; PAH = polyaromatic hydrocarbons; PBB = polybrominated biphenyls; PCB = polychlorinated biphenyls; PCDF = polychlorinated dibenzofurans; VCD = 4-vinylcyclohexene diepoxide.

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assessments. Investigators are doing the best they can using what data are available, or readily gathered, but for most research questions, cross-sectional approaches cannot adequately address the complex nature of risks associated with endocrine disrupting compound exposure.

Clinical and Public Health Implications

In light of the limitations of existing data, the biomedical literature does not provide consistent evidence for the presence

or absence of risk for particular contaminants. Overall, the strongest evidence of environmental contaminant exposures interfering with healthy reproductive function in adult females is for heavy metals, particularly lead. Compounds that can influence the normal balance of hormones, including many pesticides and persistent pollutants, also appear related to risk for many adverse reproductive outcomes. For the most part, this review has found the greatest concerns with compounds that interfere with hormone homeostasis rather than exposures leading to system failures or frank structural

organ damage. Many of the compounds reviewed have demonstrated effects in both human and animal models leading to changes in hormone formation, receptor status, function, and regulatory processes.

From a clinical perspective, most modifiable risk appears to be associated with exposures specific to unique populations (contaminated fish consumers) or occupational groups (pesticide applicators). Questions about such exposures may not come up in a typical patient history, but clinicians should consider them during prepregnancy counseling or if patients encounter reproductive difficulties. As part of promoting a healthy lifestyle, physicians can comment on hobbies and occupational exposures as well as encouraging patients to avoid unnecessary exposures. Where hazards are known or suspected, for example with applying pesticides, people should take any recommended precautions and follow label instructions. Patients may also avoid common pesticide exposures by using integrated pest management and consuming organic products rather than conventionally produced food.

From a public health perspective, we should remember that reproductive health is couple-dependent, and is a culmination of a lifetime of experiences and exposure scenarios. The interdependence of reproductive health endpoints calls for better integration of longitudinal studies with multiple endpoints.

FUTURE RESEARCH DIRECTIONS

The public is concerned about these potential hazards, but the knowledge base is piecemeal and does not address the major concerns in a systematic way. Wherever possible, research efforts should be coordinated across the lifestage using longitudinal study designs. To maximize efficiencies, researchers should cooperate with each other and pool data across studies and follow up existing cohort datasets, thus allowing investigators to assess offspring health and later life health events for original cohort members. The field would definitely benefit from increased attention to improved research methods. Some of the recent reports lack adjusted estimates, relied on very small number of subjects, and produced inconclusive results. Small suggestive studies are useful when there is no data to suggest a hazard, but also serve to (perhaps unnecessarily) raise public concern and add “noise” to the already murky field of environmental effects on reproductive health. Serious investigations with rigorous measures are what is really needed.

In light of the findings presented here, more research on the impact of endocrine-active compounds in current use, such as phthalates, flame retardants, and perfluorinated acids is warranted. We should build on data from studies of hormone active pharmaceuticals such as birth control methods and ovulation stimulators for estimates of high dose effects. Finally, research is needed to understand how the endocrine system and markers of healthy reproductive function are influenced by the complex mixtures of environmental toxicants routinely encountered by women.

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