Biennial Review of Infertility

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Editors

Biennial Review of Infertility

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We dedicate this initial volume of Biennial Review of Infertility to William Harvey, Min Cheuh Chang, Robert Edwards, Patrick Steptoe, Howard and Georgeanna Jones, and the many other pioneering clinicians and scientists on whose foundation we continue to build improved care for the infertile couple.

Preface

Infertility is a common and profound medical disease. The speed at which our understanding of reproductive medicine grows and new technologies emerge is accelerating and daunting. The objective of this book is to present important and cutting edge topics relevant to infertility in a single volume accessible and applicable to all medical specialties involved in the care of infertile couples. We have strived to select respected, evidence-based experts as authors to present each topic in a clear manner that will benefit both clinicians and scientists.

The nature of science is that hypotheses are tested by experiment, theories are proposed, and validation studies are undertaken. Especially in medical science, study design is often, by necessity, suboptimal and the flow of resulting data may be confusing and conflicting. Therapies may be undertaken without validation, and essential science is delayed by the desire to treat the patient and stay at the cutting edge of the industry. These issues are not unexpected, but may cause confusion and ultimately are not helpful for the infertile couple. Therefore, we have specifically focused each chapter on evidence-based medicine. Despite this strong focus, limitations of our published literature exist. Where such limitations exist, we have endeavored to provide a balanced view of existing information that is clinically relevant for the evolving areas of our specialty. Additionally, we have introduced a section highlighting emerging controversies in the field of reproductive medicine in which contrasting points of view are presented. It is our hope that this section will stimulate further studies to improve understanding of the topics presented.

During clinical evaluation and therapy, an infertile couple will likely interact with a variety of health care professionals, including gynecologists, reproductive endocrinologists, urologists, andrologists, embryologists, laboratory technicians, nurses, and therapists. Indeed, appropriate patient care rests on effective communication and collaboration among such a team of experts. It has been our pleasure, as co-editors of this book, to work together as a diverse group of specialists to bring together the topics discussed herein. Our aim is that this book can act as a biennial tool to provide an ongoing appraisal of current knowledge, and to foster communication and collaboration among all those working to help couples resolve their infertility.

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Section I
Female Infertility

Environmental Factors Affecting Female Infertility

Victor Y. Fujimoto and Linda C. Giudice

Abstract There is increasing concern about the effects of environmental contaminants on reproductive health. While there are limited clinical data regarding most chemical exposures and human reproduction, studies in laboratory animal models and wildlife underscore the vulnerability of the reproductive system to many environmental insults at different times of development and across the life cycle. Here, we review data implicating select environmental contaminants in compromised reproductive capacity in animals. We also review epidemiologic data in humans that suggest roles for environmental contaminants in reproductive dysfunction and infertility.

Keywords Environmental contaminants • Reproduction • Organic and inorganic exposures • Embryo toxicity • Oocyte toxicity

1 Introduction

The emerging research area of environmental and reproductive health is gaining increasing attention in the scientific and medical communities, as well as patient advocacy groups, as there is an escalation of studies citing the adverse effects of environmental exposures on human and mammalian reproduction (1–4). Several environmental chemicals that display endocrine-disrupting potential have been shown to demonstrate alterations in hormone signaling and effects on reproductive tract development and function in vivo and in vitro (5). Many environmental chemicals are inadvertantly introduced into the human system by normal daily living activities through food, water, air, personal care products, toys, infant teethers, dental sealants, and the like. For example, patients who consume higher amounts of seafood are at increased risk for the bioaccumulation of methyl mercury and polychlorinated biphenyls (PCBs) (6, 7). These and other chemicals discussed in this chapter are ubiquitous in the environment and are present in fish, wildlife, human adipose tissue, blood, and breast milk. One clear example of reproductive toxicity involves mercury. Administration of methyl mercury adversely affects the embryo viability in pregnant mice with a subsequent reduction in litter sizes (8). There are other examples of compromised embryonic development and blastocyst formation in animal models where oocytes and embryos are exposed in vitro to concentrations of PCBs, dichlorodiphenyltrichloroethane (DDT), hexachlorocyclohexane (HCH), and methoxychlor (MXC) (9–11).

While there are many classes of environmental contaminants, here we focus on the effects of smoking, pesticides, heavy metals, and a variety of other chemicals on mammalian gametogenesis and embryogenesis, as well as human clinical/epidemiologic reproductive outcomes. Where possible, we also discuss biologic mechanisms regulating these effects. There is a broad body of literature detailing environmental contamination and reproduction in avian and amphibian models, which is not included in this chapter but is available for review (12–14). Fecundity and early embryo risk are discussed; however, issues around pregnancy and birth outcome risks are not included in this chapter, as they have been comprehensively reviewed (15). In addition, the scope of effects from environmental exposures in

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female reproductive health and disease, i.e., endocrine disruption, gynecologic disorders, and pregnancy outcomes, is substantial and have been the subject of several recent comprehensive reviews (1–3). All the sections included here were developed through the specific environmental exposure of interest and include exposures during different developmental/adult life stages with the following categories of exposure: (1) cigarette smoking and polycyclic aromatic hydrocarbons; (2) agricultural and residential pesticides; (3) inorganic heavy metals; (4) bisphenol A; (5) polychlorinated and polybrominated biphenyl compounds; (6) DDT and DDE; and (7) dioxins. The final section discusses our current understanding of the role of the aryl hydrocarbon receptor (AhR) as a mediator of halogenated aromatic hydrocarbon contaminant effects in mammalian reproduction.

2 Cigarette Smoking and Polycyclic Aromatic Hydrocarbons

One in three adults smokes cigarettes (16). The demographic distribution of cigarette smokers varies widely, with the highest percentage of cigarette smokers in Europe and Asia. The environmental contaminants identified in cigarette smoke number approximately 4,000 chemical compounds (17). Cigarette smoking has long been known to induce changes in reproductive function, with effects on both oocytes and embryos. While there are behavioral changes in women that occur once they identify themselves to be pregnant, including cessation of smoking, many women remain relatively unaware of the negative impact that cigarette smoking can have on their and their offspring's reproductive health. Several epidemiologic studies and reviews have demonstrated a clear association between smoking and reduced fecundity (18–20). The time to pregnancy (TTP) is consistently delayed in smokers compared to nonsmokers (21). The American Society of Reproductive Medicine has produced a patient fact sheet on smoking and infertility and practice guidelines with a position statement on smoking and reduced fecundity, discouraging smoking in women who are considering pregnancy or attempting to conceive (22). Several systematic reviews and meta-analyses of the literature on smoking and infertility have been published, which provide a consistent negative association between female cigarette smoking exposure and fertility potential (22–24). Ex-smokers appear to have a similar fecundity rate, compared to nonsmokers, suggesting that active exposure to chemicals in cigarette smoke during the follicular phase and/or luteal phase of the menstrual cycle inhibits normal reproductive processes (19). Further evidence of the negative association of cigarette smoking by females on reproductive results comes from in vitro fertilization (IVF) data (25–29). Zenzes et al. found an increased proportion of diploid oocytes recovered during IVF and a decreased proportion of mature oocytes with cigarette smoking (29, 30). There may also be contributing endometrial dysfunction as demonstrated by Soares et al., who showed that lower pregnancy rates were associated with heavy cigarette smoking in an oocyte donation–recipient model (31). A recent study found that women exposed to secondary cigarette smoke also have lower IVF pregnancy outcomes, similar to women who smoke cigarettes directly (32). A comprehensive review of the effects of smoking on human gametes and embryos has recently been published (33).

There is also evidence that women who smoke cigarettes have an increased risk of spontaneous miscarriage (23, 34, 35). However, other studies have not clearly demonstrated an association between cigarette-smoking and risk of spontaneous abortion (36–40). In addition to the risk of spontaneous miscarriage, multiple studies have demonstrated an increased risk of ectopic pregnancy associated with active cigarette smoking (41–44). Mechanistically, tubal motility and ciliary function have been implicated as targets of cigarette contaminant exposures (45–49).

Cumulative evidence suggests mechanisms underlying adverse actions of the chemicals in cigarette smoke on ovarian, tubal, and endometrial function. One of the challenges in understanding the biologic mechanism of cigarette smoking on reproductive processes is the large number of chemicals found therein. While many of the chemicals have been poorly studied, one constituent of cigarette smoke that has been well studied is cotinine, a stable metabolite of nicotine. Cotinine levels in humans correlate strongly with tobacco consumption (50). Both cotinine and cadmium levels have been detected in human follicular fluid (FF), with higher levels in smokers than in nonsmokers (51–53). Additionally, other toxins known to exist in cigarette smoke include the class of compounds known as polycyclic aromatic hydrocarbons (PAHs) (54). PAH compounds of interest

include 9,10-dimethylbenzanthracene (DMBA), 3-methylcholanthrene (3-MC), and benzo[*a*]pyrene (BaP) (see Fig. 1). BaP exposure reduces litter size and decreased survival of fetal pups in a dose-dependent fashion (55, 56). PAH compounds affect granulosa cell function and have been indirectly associated with the development of a variety of ovarian tumors (57–59). BaP levels and DNA adduct formation have been detected in luteinized granulosa cells recovered from IVF FF and correlate with cotinine levels, suggesting an increased risk in granulosa cell DNA damage with cigarette smoking (60). Various polymorphisms in metabolic genes, including CYP1A1 and GSTT1, have been associated with differences in fetal birth weight restriction associated with cigarette smoking (60).

The most profound effect of PAHs via cigarette smoking on female reproduction may be the decline in ovarian reserve associated with its exposure. This observation is consistent with the association of cigarette smoking with an earlier age at menopause (61–63). Sharara et al. described diminished ovarian reserves in women who smoke cigarettes on the basis of abnormal clomiphene challenge testing (64). Several studies have confirmed an association between cigarette smoking and elevated basal follicle-stimulating hormone (FSH) levels independent of age (65–67). DMBA, 3-MC, and BaP were all found to be ovotoxic, resulting in significant destruction of primordial and primary follicles in mice and rats (68–71). Mechanistically, there is evidence that PAH-induced reduction of primordial follicles operates via the AhR-regulated Bax expression (72, 73). That said, it is not yet clear whether ovarian antral follicle pools are diminished in humans in response to cigarette smoking when adjusted for maternal age (67, 74). Ovarian response, defined by the numbers of mature oocytes retrieved, appears to be less in cigarette smokers than nonsmokers, although age-adjusted correlations were not performed (26). Collectively, the

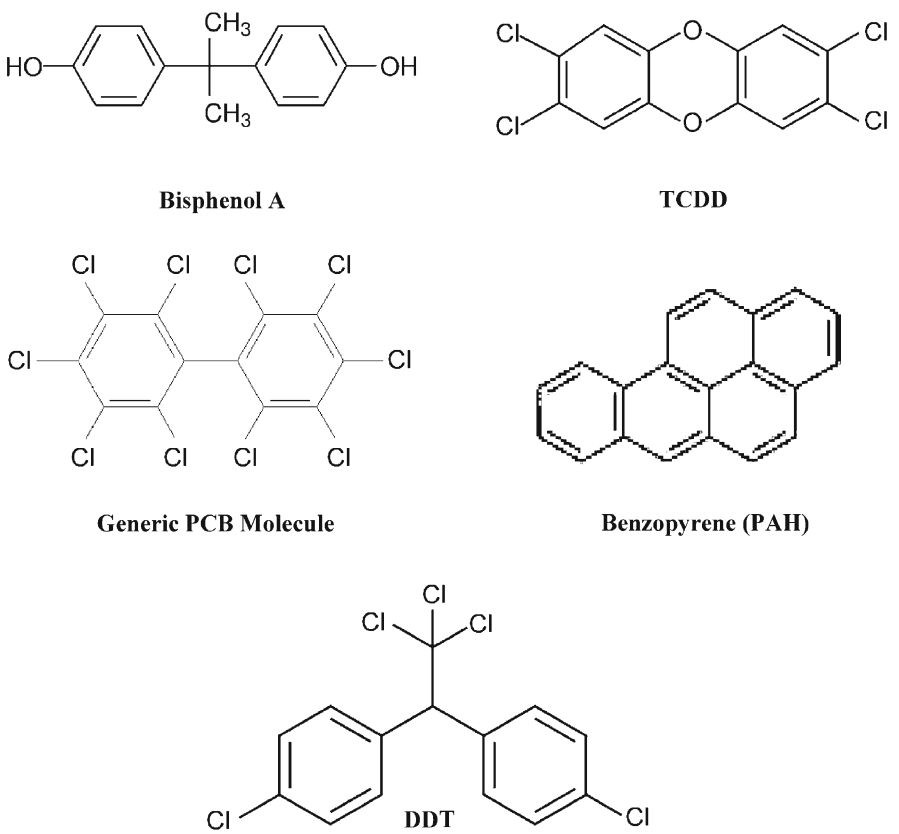

Fig. 1 Organic chemicals ubiquitous in the environment and responsible for reproductive effects

evidence in the literature points toward a negative impact of cigarette smoking on ovarian aging processes.

The Barker hypothesis proposes that in utero fetal exposures to nutritional (and by extrapolation, environmental) contaminants can manifest in adult life as clinical disease or altered state of health (75–77). This hypothesis with regard to environmental contaminants is supported by the recent study by Jurisicova et al., in which a decrease in the fetal ovarian follicle pool exposed to PAHs during gestation was observed and demonstrated to be via activation of the cellular apoptotic pathway mediated by the AhR (78). Furthermore, xenotransplanted human ovaries responded to PAHs similarly (78). These observations are consistent with the reduced fecundity seen in women exposed in utero to maternal cigarette smoking (79).

3 Agricultural and Residential Pesticide Exposures

Considerable attention has been given to the possibility that heavy pesticide exposure may cause increased reproductive difficulties. Numerous studies have addressed a possible relationship between agricultural and household pesticide use and the risk of spontaneous abortion. Although the data to date are inconclusive with regard to an association of pesticide exposures and increased risk of spontaneous abortion (80–89), a study by Greenlee et al. suggests an association between direct mixing and application of pesticides by reproductive-aged women and their likelihood of infertility within two years of direct contact with pesticides (90).

Biologic evidence has been provided implicating pesticides in affecting early embryogenesis in a study where six herbicides (atrazine, dicamba, metolachlor, 2,4-dichlorophenoxyacetic acid (2,4-D), pendimethalin, and mecoprop), three insecticides (chlorpyrifos, terbufos, and permethrin), and two fungicides (chlorothalonil and mancozeb) in combination or sometimes individually adversely affected the development of murine blastocyst embryos (91). In the early 1990s, studies demonstrated that carbendazim, the active metabolite of benomyl, a systemic benzimidazole fungicide that was banned in the United States in 2002, had direct effects on the meiotic spindle assembly of the murine oocyte. Perreault et al. found an increase in preimplantation and postimplantation pregnancy losses after acute carbendazim exposure in female hamsters during the proestrus period (92). As a result of further investigation into the etiology of this infertility causation, Zuelke and Perreault subsequently demonstrated that carbendazim induced meiotic arrest within the oocytes (93). Jeffay et al. further elucidated the carbendazim effect by inducing an arrest of preimplantation development of murine embryos to the blastocyst stage with acute carbendazim exposure in the female hamster during the proestrus–estrus transition (94). Can and Albertini were able to interrupt the meiotic spindle assembly of murine oocytes using a benzimidazole derivative, methyl 2-benzimidazolecarbamate, lending further evidence to its mechanism of action (95). While benomyl was banned from use in California in 2002, there is evidence of the persistence of carbendazim in human FF in women undergoing IVF (Fujimoto, unpublished data).

In 1993, a case–control study assessing a cluster of Down syndrome infants with an incidence of 27% in a small Hungarian village suggested trichlorfon insecticide exposure as the etiology (96). Apparently, a high consumption of fish contaminated with trichlorfon around the time of conception was associated with high meiotic II error rates, increased miscarriage, and Down syndrome offspring in exposed individuals. Yin et al. subsequently confirmed in mouse in vitro matured oocytes that trichlorfon adversely affects normal spindle formation during meiosis (97). Recent evidence suggests that pesticides can influence aromatase activity in the human choriocarcinoma JEG-3 cell line (98). These examples illustrate the potential sensitivity of the mammalian oocyte, surrounding cumulus cells, and the early embryo to pesticide exposures and lend biologic plausibility to adverse effects on human gametes and embryos.

4 Inorganic Heavy Metal Exposures

There are only a few studies on the effects of toxic heavy metals (arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg)) on mammalian reproduction. Several animal and human studies have linked Hg exposure to reproductive toxicity. Hg has been shown to be embryotoxic in animal studies (8, 99). In addition, it has been linked to an increased risk of spontaneous abortion and

birth defects (100). Some studies of male infertility have demonstrated the potential effects of Hg on human seminiferous epithelium in the testis, but the data are controversial (101). Relatively few studies on Hg and female infertility have been published. Rowland et al. found decreased fertility among female dental assistants exposed to Hg vapor (102). In another study in Hong Kong, infertile Asian couples undergoing IVF were found to have significantly higher blood Hg concentrations than the control group and these higher concentrations were associated with higher seafood consumption (103).

There are several environmental sources of Hg, but the aquatic food chain is an important source of bioaccumulation. Seafood intake has been shown to contribute to the bodily accumulation of Hg, and Hg consumption is considered a health risk. The Environmental Protection Agency and the National Research Council recommend blood Hg levels <5.0 μg/L or hair level <1.0 μg/g (104). Populations that have a high intake of fish are at particular risk of Hg exposure, including the Nunavik Inuit communities residing in Northern Quebec and residents of the Faroe Islands and New Zealand, which has raised concerns over childhood neurodevelopmental delay in those populations (105–108). A San Francisco-based study found that patients with diets high in commercial fish consumption had blood Hg levels that far exceeded these recommended levels (7). Recently published data of the National Health and Nutrition Examination Surveys (NHANES) reveal that Asians and Pacific Islanders have significantly higher Hg than other ethnicities surveyed (109, 110), indicating that they are potentially at greater risk to the reproductive toxic effects of methyl Hg.

In addition to Hg in fish, there are high levels of Cd in cigarette smoke and Pb, Hg, and As contamination of herbal products from Asia (111–114). A specific example of herbal product contamination is ginseng extracts, of which 80% were found to have detectable levels of various pesticides and benzene derivatives (111). A case of Pb poisoning has recently been reported as a direct result of herbal product consumption during infertility treatment (115). It is currently not clear whether detectable exposures of toxic metals such as As, Pb, Hg, and Cd have deleterious effects on human reproduction. These heavy metals have all been detected in human FF (116–118). A recent IVF-based study assessing Cd, Pb, and Hg levels found a negative association between lead levels and fertilization outcomes but no effects were seen with Hg or Cd (116). There is evidence that both As and Cd adversely affect murine blastocyst development with increased apoptotic changes possibly via oxidative stress mechanisms (119–123). It should be noted, however, that further studies are needed to clarify the roles of various heavy metals in female reproduction.

5 Bisphenol A Exposure

Bisphenol A (BPA) is gaining considerable attention as an environmental chemical that may have adverse effects on human health and disease. The chemical name of bisphenol A is 2,2-bis(4-hydroxyphenyl) propane (see Fig. 1) (124). BPA is produced in large quantities (more than £6 billion per year) for incorporation into various resins and plastics (e.g., polycarbonate) (124). The exposure to BPA is ubiquitous, penetrating many aspects of daily living primarily through dietary consumption. A consensus statement was issued in 2007 by the Chapel Hill Bisphenol A expert panel on the relationship between BPA and human health effects (124). BPA has been shown to have endocrine-disrupting effects through steroid receptor binding. BPA binds with weak affinity to the nuclear estrogen receptor, although recent evidence suggests it may act to induce physiologic responses through cell membrane estrogen receptors in low picogram per milliliter concentrations (125). In humans, serum BPA levels have been measured within the nanogram per milliliter range (126, 127). Urinary concentrations of BPA have been measured in the microgram per liter range (128, 129). There is currently a debate as to whether the low exposure levels of BPA in humans have significant reproductive biologic effects (125, 130, 131).

The adverse female reproductive effects of BPA exposure have been described primarily on meiotic aberrations in the oocyte. Studies are based for the most part on mammalian models with little clinical evidence thus far available. There are currently four studies that detail our current understanding of BPA effects on oocyte nuclear health. In 2000, Takai et al. published their work on the effects of BPA on early embryo development (132). Two-cell mouse embryos were cultured with BPA with or without tamoxifen, a selective estrogen receptor modulator, and evaluated for blastocyst advancement. At 100 μM concentration

of BPA, decreased blastocyst formation was observed and negation of the effect in the presence of tamoxifen, suggesting an estrogen receptor–mediated effect. At nanomolar concentrations of BPA, the opposite effect was seen with increased murine blastocyst formation.

Several studies have demonstrated that BPA interferes with microtubule assembly in the cultured Chinese hamster lung V79 cell line (133, 134). A direct link between BPA and murine aneuploidy was first reported by Hunt and colleagues (135). In this landmark study published in 2003, a dramatic increase from 1–2% to 40% was observed in chromosomal alignment defects in the first meiotic spindle. Furthermore, a high rate of aneuploidy (hyperploidy) was also observed in these animals. This increase was ultimately traced and attributed to the leaching of BPA from water bottles and damaged cages in which the female mice were housed during the final stages of oocyte maturation. Thus, in adult female mice completing their estrus cycles, an association between BPA exposure and meotic spindle abnormalities in their oocytes was demonstrated.

Further study of the effects of BPA on meiotic cell cycle progression was reported by Can et al. in 2005 (136) who found that mouse cumulus–oocyte complexes exposed to BPA exhibited a dose-dependent delay in the transition of oocytes from metaphase I to metaphase II. Fluorescent-labeling of oocytes with α + ß-tubulin and pericentrin, together with confocal imaging of the in vitro matured oocytes exposed to BPA, revealed disturbed microtubular spindle structure and pericentriolar compaction and dispersion, compared to control oocytes. In addition, the absence of chromosomes in the first polar body was commonly seen in the BPA-treated oocytes. The doses of BPA required to disrupt the meiotic spindle assembly in oocytes are lower than those required to disrupt the mitotic spindle assembly of Chinese hamster V79 cells (133, 134, 136). Can and Semiz previously demonstrated that diethylstilbestrol, a synthetic estrogen, also disrupted the progression of metaphase I oocytes to metaphase II, with fragmentation and loosening of the meiotic spindle assembly (137). BPA also induces apoptosis in murine ovarian granulosa cells. In addition, the alkylphenol, *p*-tert-octylphenol, which has endocrine-disrupting properties via the estrogen receptor, reduces bovine oocyte nuclear maturation, thereby preventing meiotic progression (138).

Perhaps the most intriguing study thus far with respect to the role BPA on oocyte integrity was published in 2007 by Susiarjo et al., in which murine fetal oocytes exposed to BPA during gestation were similarly found to have abnormal pachytene associations and abnormalities in synaptonemal complex structure, compared to unexposed murine fetal oocytes, as determined by MLH1 and SCP3 immunostaining (139). Similar to PAHs from cigarette smoking, this observation lends further support to the Barker hypothesis that in utero exposures may influence future reproductive outcomes. These data would suggest that there may be a transgenerational impact of BPA exposure in utero. Furthermore, when oocytes of 4–5 week-old pups exposed to BPA were analyzed, there was a higher rate of aneuploidy; specifically, about 40% of all oocytes were aneuploid, compared to an unexposed rate of 1.8% (139). The proposed mechanism for the effect of BPA on altering the synaptonemal complex of murine fetal oocytes, offered by these investigators, involves the estrogen receptor ß as a potential site of interaction with BPA, or at least a final common pathway for disruption. This is based on a similar meiotic phenotype in prophase fetal oocytes of ßERKO–/– mice with similar rates of synaptonemal aberrations (57%), compared to those of the BPA-exposed female murine fetus (52%).

While these murine studies collectively provide substantial evidence towards a BPA-induced effect on oogenesis and increased meiotic errors at various stages of oocyte nuclear maturation, there is little evidence to support this concept in humans. The only published clinical study comes from Japan, in which 45 patients with a history of three or more first trimester miscarriages without uterine anomaly or blood karyotype abnormality (study group) and 32 healthy nonpregnant women without prior pregnancy loss (control group) underwent serum BPA testing (140). Mean serum BPA levels were higher in the study group compared to the control group (2.59 vs. 0.77 ng/mL, $P = 0.024$), showing that serum BPA is associated with recurrent miscarriage (140). However, the limitations of this study include the short half-life of BPA that can result in substantial variability of BPA measurements, the lack of timing of BPA measurements within relevant biologic timeframes (such as during the lutenizing hormone (LH) surge when BPA exposure is most likely to affect the meiotic transition from metaphase I to metaphase II), the statistical methodology used, and

the different demographics utilized for recruitment of patients and control subjects. Thus, it is currently not known to what extent BPA exposures affect human oocyte health, despite compelling murine studies. Clearly, well-designed studies are needed to establish with confidence an association of BPA exposure with aneuploidy risk and reduced reproductive potential in women.

6 Polychlorinated and Polybrominated Biphenyl Compound Exposures

This category of environmental toxins represents a broad family of various industrial contaminants that include PCB compounds, polychlorinated dibenzo-*p*-dioxins (PCDDs), and polychlorinated dibenzofurans (PCDFs). These chemicals are ubiquitous and persistent in the environment because of their chemical stability, lipophilic character, and low water solubility (141). Although banned from production in most countries in the 1970s, PCBs have received increasing attention as environmental contaminants of relevance to reproductive outcomes. The food chain is the primary source of human contamination with 209 congeners of these halogenated aromatic hydrocarbon compounds (see Fig. 1) (142). Because of their lipophilic nature, bioaccumulation occurs within an organism, which is magnified in each predator. PCB congeners are classified by the United States Environmental Protection Agency as probable human carcinogens of medium carcinogenic hazard. The first report of PCBs causing reproductive harm came from a study based in the Wassen Sea, Netherlands, in which a decline in the seal population was traced to reduced litters because of PCB and DDE contamination (143). Human consumption of sport-caught fish provides high exposure to PCB congeners (144, 145) and results in measurable levels of PCBs in serum and urine (146–149). Maternal serum PCB concentrations have been documented during critical windows of development including the periconception interval and early pregnancy (150). PCB levels are detectable within the human FF (151–155). A study originating from the New York Angler Cohort in the Great Lakes area demonstrated an association between maternal fish consumption and reduced fecundability (156). However, other studies have not revealed associations between maternal fish consumption and time-to-pregnancy (TTP) outcomes in areas with high PCB exposures (144, 157, 158). Given the well-documented contamination of the Great Lakes ecosystem by PCBs, dioxins, heavy metals, and pesticides, it has been hypothesized that the observations made about maternal fish consumption and increased TTP may be causally related to exposures to these various toxins (159).

Cohort studies assessing the risk of spontaneous miscarriage have found no associations with PCB exposures (160–162), and there are no studies addressing PCB exposures and reproductive outcomes within an infertile population. PCBs have also been implicated as a cause of fetal growth restriction identified with maternal contaminated fish consumption (163, 164). Beyond these limited studies focusing on fecundity and maternal fish consumption, no other evidence exists in epidemiologic studies to support the effect of contaminated fish consumption and poor reproductive potential.

Polybrominated biphenyl compounds (PBBs) are structurally similar to PCBs, except for a bromine substitution. In 1973, PBBs entered the human food chain in the United States via meat and dairy products inadvertently contaminated with PBBs (165). By recruiting exposed women identified through a registry, there was no increased risk of spontaneous abortions in women with PBB levels above 6.5 ppb, compared to women below the limit of detection (166). Associations between PBBs and infertility await further investigation.

Several studies in mammalian models demonstrate effects of PCBs on ovarian function, oogenesis, and embryogenesis. Some studies have demonstrated a disruption of both estrus and menstrual cycles (167–170). Kholkute et al. demonstrated that several PCB mixtures negatively affect the fertilizability of murine oocytes (171–173). Pocar et al. demonstrated disruption of bovine oocyte maturation with PCB exposures as low as 0.01 mg/mL and impaired fertilization and increased polyspermy at 0.001 mg/mL (174). The PCB, 3,3′,4,4′-tetrachlorobiphenyl, was also found to decrease fertilization potential in murine oocytes when female mice were fed a diet containing the PCB, tetrachloro-biphenyl (TCB), within two weeks of pairing (175). Pocar et al. also showed a dose-dependent effect on reduced bovine blastocyst formation from PCB exposures (174). Effects of organochlorine compounds on in vitro porcine oocyte maturation, fertilization, and early embryonic development (10) reveal that when

cumulus oocyte complexes (COCs) are isolated, matured, fertilized, and cultured in the presence of various concentrations of an organochlorine mixture that includes the PCBs, Aroclor 1260, Aroclor 1254, PCB 126, and 3,3′, 4,4′-tetrachlorobiphenyl among other non-PCB compounds, there is marked functional disruption. These include dose-dependently reduced cumulus expansion and decreased blastocyst formation (10). A 20% reduction in blastocyst formation was also noted in female rabbits given the PCB, Aroclor 1260, three times a week at 4 mg/kg body weight dosage (176). Low concentrations (1 pg/mL range) of Aroclor 1254 disturbed bovine oocyte fertilization with increased polyspermy and reduced blastocyst formation (174). In the in vitro matured bovine oocyte model, subsequent blastocyst formation was reduced using PCB 126 in exposures ranging from 1 to 100 pg/mL (11). Thus, there is clear evidence in various mammalian models that oocyte competence and early embryo development can be compromised by exposure to PCBs.

While the mechanisms responsible for these observed effects of PCBs on early embryo development are unknown, there is evidence that PCBs have proinflammatory properties that increase oxidative stress via the AhR (177–180). There is evidence that PCB-like compounds act via the AhR, a ligand-activated transcription factor, to affect murine ovarian weight and ovarian cyclicity (181, 182). However, Schmidt et al. identified AhR −/− mice to be fertile without compromised reproduction, raising the question of whether PCB effects on reproduction are mediated via other mechanisms (183). Further evidence against a role for the AhR being involved in the embryotoxic effect of PCBs is provided by Kietz and Fischer, who demonstrated changes in rabbit blastocyst gene expression changes independent of AhR expression after exposure to PCBs (184).

7 DDT and DDE Exposures

1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) is an insecticide that is metabolized to 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) – a persistent organochlorine pollutant (see Fig. 1) (185). Although banned in the United States in 1972, the scope and persistence of these compounds in our environment are underscored by the finding that DDT and DDE comprise 84% of the analyzed pesticide concentrations in the surface sediment layer (70 cm) of San Francisco Bay (186). This buildup clearly represents the legacy left behind by the substantial utilization of DDT from the mid-1940s through the mid-1970s as an agricultural pesticide in California. Similar to PCB exposures, DDT and DDE were present in the serum and urine of pregnant women from the San Francisco Bay area participating in the Child Health and Development Study of California (146–149, 187). Also similar to PCBs, DDT and DDE are lipophilic, slowly metabolized chemicals that accumulate in human adipose tissue (188). The persistent nature of DDE in humans is demonstrated by studies that show similar levels of DDE compared to those conducted 30 years earlier (189, 190). In a study based in Ontario, Canada, approximately 50% of IVF patients had detectable levels of DDE in serum and FF with mean levels considerably higher than any PCBs (155). In the San Francisco Bay area population, all IVF patients tested had detectable levels of FF DDE (Fujimoto, unpublished data).

DDE exposure is associated with an increased risk of spontaneous abortion (189, 191, 192). Korrick et al. found a positive association between serum DDE levels and spontaneous abortion in this case–control study, but this study was limited by the variable time frame of blood collection from the index pregnancy outcome (189). Sera from pregnant women in the Collaborative Perinatal Project from 1959 to 1965 were tested for DDE and related to prior spontaneous miscarriage history, adjusted for age, race, and smoking, with DDE levels ranging from 0 to 60 mg/L (191). An increased serum DDE level was positively associated with a fetal loss history but was limited also by the retrospective history of pregnancy loss (191). Venners et al. published a prospective study in a Chinese population of reproductive-aged, newly married women (192). Daily urine samples were collected and measured for DDT and human chorionic gonadotropin (hCG) levels, which revealed an exposure–response association between preconception DDT levels and subsequent early pregnancy losses (192). However, DDE and TTP studies have not consistently revealed differences in fecundity as a result of DDE exposures (193, 194). By Pearson correlation analysis, Younglai et al. demonstrated a negative association between serum and FF levels of DDE and IVF fertilization, but

no effect was found on pregnancy outcomes (155). In a small cohort, higher serum DDE levels in women undergoing IVF were associated with reduced pregnancy rates (but not significant likely due to a lack of power) (195). An interesting study published in 2003 demonstrated reduced fecundability in daughters of mothers who were exposed during pregnancy to high levels of DDT and DDE between 1960 and 1963, suggesting an in utero effect of this endocrine disruptor on the fetal reproductive axis, similar to BPA (196).

A biologic mechanism for the effects of DDT and its metabolite, DDE, on reproductive potential remains elusive. However, studies on the effects of DDE on granulosa cells suggest endocrine-disrupting properties. DDE decreases steroidogenesis in luteinized granulosa cells but increases VEGF and IGF-1 expression in the ovarian follicle (197–200). Incubation of murine embryos with low doses of DDT reduces the growth of early stage embryos and subsequent blastocyst development, with increased apoptosis (201). A similar observation was made in bovine embryos exposed to DDT, with a reduction in blastocyst formation (9). This effect of DDT on murine blastocyst development was reversed by the addition of an estrogen receptor antagonist (202). However, a subsequent study did not reveal any effect on implantation rates or number of pups per dam after incubation of murine embryos with DDT (203). It is possible that the negative effects of DDT and DDE on early embryogenesis may be acting via oxidative stress pathways (204, 205).

8 Dioxin Exposures

Dioxins represent a class of organic chemicals that are structurally related to PCBs (see Fig. 1). Similar to PAHs and PCBs, dioxins are believed to activate AhR ligands with downstream gene activation and expression (206). The clinical evidence for dioxin exposure and reproductive health comes mainly from the Seveso Women's Health Study, which studied an Italian village population north of Milan exposed to high levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) from a chemical plant explosion that released ~30 kg of TCDD into the atmosphere in 1976 (207). The measurable serum levels of TCDD in Seveso residents ranged from 2.5 to 56,000 ppt, with a background nonexposed level of 20 ppt (208). Unintended human exposures to TCDD generally occur via consumption of contaminated food products and air inhalation around industrial waste processing plants. TCDD has been classified as a human carcinogen by the International Agency for Research on Cancer and displays endocrine-disrupting properties (209, 210).

The clinical relevance of dioxin exposures to human reproduction is still unknown. A case–cohort study of Seveso women exposed to high levels of TCDD found a nonsignificant association with surgically diagnosed endometriosis (211). Furthermore, there is evidence in the nonhuman primate model which indicates that chronic exposure to TCDD increases the risk of endometriosis, with severity of disease that is dose dependent (212, 213). However, the association between TCDD exposure and clinically diagnosed endometriosis remains controversial in humans (214–219). Nonetheless, functional AhR receptors that are dioxin responsive are expressed in human endometrial stromal cells and endometriosis implants (220). There are no studies currently in the clinical literature that directly address the role of dioxins in human reproductive potential, and although TCDD is present in human FF (221), there are no data on direct effects of TCDD on oocyte development and function.

There are several studies, however, worthy of mention within the TCDD mammalian reproduction literature. For example, TCDD can alter murine estrous cyclicity and ovulatory events (222, 223), and TCDD administered to pairing female hamsters lengthens the time to first litter in a dose-dependent fashion (224). TCDD exposure increases the cavitation rates of murine preimplantation embryos, with accelerated differentiation (225). There is also evidence that TCDD exposure during preimplantation development alters gene expression of murine blastocysts and the methylation status of the murine imprinted genes H19 and Igf2 (226, 227). Also, when murine embryos are incubated with TCDD in concentrations found in human FF (1–5 pM range) they responded with stage-specific effects of lower eight-cell development but accelerated blastocyst development within surviving embryos (221). Murine maternal exposure of environmentally relevant doses of TCDD during the periconception period does not affect ovulation, fertilization efficiency, or embryo survival, but rather results in disrupted nuclear and cytoplasmic profiles of preblastocyst embryos (228).

Early fetal loss has been demonstrated with maternal TCDD exposure in several different mammalian models, including the primate, possibly owing to effects on uterine decidualization (229, 230). There is also evidence that TCDD acts as an endocrine disruptor to reduce estrogen biosynthesis within the ovarian follicle via actions on 17,20 lyase activity of the P450c17 enzyme complex (231). TCDD may influence ovarian reserve via the AhR receptor activation pathway, similar to PAHs (232, 233). Collectively, these studies suggest that dioxins may have direct effects on oocyte and early embryo development as well as endometrial differentiation.

9 Aryl Hydrocarbon Receptor in Reproduction

As has been mentioned earlier in the sections on cigarette smoking and PAHs, PCBs, and dioxins, AhR-mediated pathways appear to be important in cell signaling with these lipophilic organic chemicals (halogenated aromatic hydrocarbons) which are considered important activating ligands that bind to AhR intracellularly (234). This complex disassociates within the cell nucleus and dimerizes with AhR nuclear translocator (ARNT) to transform into a highly active transcriptional factor that regulates the transcription of cytochrome P450A1 (CYP1A1), a gene that encodes one of several xenobiotic-metabolizing enzymes (234, 235). TCDD, PAHs, and PCBs bind to AhR influencing various downstream events that effect detoxification of these lipophilic chemicals, induction of cellular apoptosis, and antagonism of normal endocrine responses (235, 236). The role of AhR in reproduction is supported by differences in fecundity between low- and high-affinity AhR (237). Bovine oocytes and surrounding cumulus cells both express AhR and ARNT (238). The use of AhR antagonists has demonstrated decreased levels of CYP1A1 in cumulus oocyte complexes with a reduced ability of bovine oocytes to undergo complete in vitro nuclear maturation (238). As discussed previously, contradictory evidence in the murine AhR knockout model exists that argues against a significant role for AhR in mammalian fertility, as the AhR−/AhR− female mouse is fertile (183). Thus, the role of AhR in fertility remains controversial, and further studies are needed to clarify the roles of halogenated aromatic hydrocarbons as ligands within the AhR-mediated pathways in reproduction.

10 Clinical Applications Summary

Evidence has been steadily accumulating regarding the effects of environmental contaminant exposures on mammalian and other animal reproductive systems. However, there remains controversy on the impact of environmental exposures on human reproduction. Large, prospective, epidemiologic-based studies are needed to address potentially subtle effects of various environmental contaminants on reproductive health. While cigarette smoking and its component chemicals as summarized in this chapter have substantial clinical and scientific data to support their effects on reducing the quality and quantity of oocytes, cigarette smoke is still unique as an environmental exposure as measured by the magnitude of research available that addresses its negative impact on human reproduction. PCBs, BPA, heavy metals, pesticides including DDT and dioxins are candidates as reproductive toxicants, with proposed biologic mechanisms for reproductive disruption, although they fall short in terms of clinical validation of their effects in the human population (see Table 1). Clearly, a concerted effort by the scientific and clinical communities must be made to further address and determine whether these chemicals adversely affect clinical reproductive outcomes before clinical recommendations can be made to limit exposures. However, before the results of these decade (or more)-long studies are conducted and the data analyzed, biologic plausibility recommends the limitation of exposures in accordance with the "precautionary principle." This principle states that if an action or policy might cause severe or irreversible harm to the public, precautionary measures shall be taken even if causal link has not been proven (239).

Table 1 Reproductive compromise associated with various environmental contaminants

	Smoking PAHs	Pesticides	Heavy metals	Bisphenol A	PCBs	DDT and DDE	Dioxins
Clinical – fecundity	+++	++	NA	+	++	+	NA
Clinical spontaneous miscarriage	++	+	+	+		+	NA
Clinical – fertility treatment outcomes	+++	NA	+	NA	NA	NA	NA
Mammalian – litter sizes	++	++		++	++	+	++
Mammalian – fertilization outcomes	NA	++	+	+++	+++		
Mammalian – embryogenesis	+++	++	+	+++	+++	++	++

No association; +, weak association; ++, moderate association; +++, strong association; *NA* no literature available to derive a conclusion

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