CHAPTER 19

Environmental Factors and Reproduction

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Introduction: Reproductive Health and the Environment

- *Documented adverse trends in reproductive health cannot be explained by genetics alone.*
- *Exposure to environmental chemicals is ubiquitous and contributes to adverse trends in reproductive health and other human diseases.*

Documented adverse trends in reproductive health in the United States include declines in fertility[1,2] and in the age of onset of puberty[3,4] and increases in rates of obesity,[5] gestational diabetes,[6,7] preterm birth,[8] and children's neurodevelopmental disorders, such as autism[9,10] and attention-deficit/hyperactivity disorder (ADHD).[8] These adverse trends are also reflected in a rise in noncommunicable diseases such as cancer, cardiovascular disease, chronic respiratory disease, and diabetes in high-, middle-, and low-income countries across the globe.[11,12] Due to the timeframe of these changes, they cannot be explained by changes in genetic makeup alone. A possible explanation is exposure to environmental chemicals.

There is mounting scientific evidence of ubiquitous human exposure to environmental chemicals and associated adverse health impacts. In response to the evidence, reproductive health leaders and other scientists, clinicians, and their professional societies have called for timely action to prevent harm.[13-24] This chapter summarizes reproductive and developmental health impacts of exposure to environmental chemicals, underlying mechanisms when known, and the role of clinicians and other health care professionals in prevention.

Definition

Reproductive environmental health addresses exposure to environmental contaminants, such as synthetic chemicals and metals (referred to collectively as *environmental chemicals* in this chapter) and their effects on reproductive health and development. Exposure to environmental chemicals can have an impact during all periods of human reproduction including fertility, conception, pregnancy, child and adolescent development, and adult health.[25]

Reproductive Health Professional Society Engagement on Environmental Health

- *Doctors in the United States and around the world have issued a call to action to prevent exposure to toxic environmental chemicals.*

The contemporary roots of physicians' organized engagement on reproductive environmental health issues date to 1957 when the American Academy of Pediatrics (AAP) became concerned about child health impacts of radioactive fallout from atmospheric testing of nuclear weapons; in the 1970s, the AAP broadened its focus to include the health consequences of exposure to environmental chemicals.[26] The issue drew the concerted attention of reproductive health professionals in the 1990s with the publication of *Generations at Risk: Reproductive Health and the Environment,* which included compiled research linking environmental exposures to adverse reproductive health outcomes and intergenerational harm.[27] In 2007, the University of California, San Francisco and the Collaborative on Health and the Environment convened the *Summit on Environmental Challenges to Reproductive Health and Fertility*, which brought together for the first time over 400 physicians, scientists, advocates, and policy makers to address reproductive environmental health science, clinical care approaches, and policy initiatives.[25] In 2009, the Endocrine Society explicated the basic science of endocrine disrupting chemicals (EDCs) and the implications for human health and disease.[17] In 2013, leading US

Abstract

Industrial chemical production has increased over the last few decades. In that same time frame, a number of adverse reproductive and health conditions have increased, including infertility, early puberty, obesity, gestational diabetes, preterm birth, children's neurodevelopmental disorders, and noncommunicable chronic diseases such as cancer, cardiovascular disease, chronic respiratory disease, and diabetes. Basic science, animal model, and epidemiologic data indicate that specific environmental chemicals can interfere with hormone levels and action (referred to as endocrine disrupters) and thus may play an etiologic role in some of these conditions. These endocrine disrupters are found in pesticides (e.g., dichlorodiphenyl-trichloro-ethane [DDT], chlorpyrifos, atrazine, 2,4-dichlorophenoxyacetic acid [2.4D]), children's toys and products (containing lead, phthalates, cadmium), materials that contact food (e.g., lining of plastic bottles or cans; bisphenol A, phthalates), building materials and electronics (e.g., brominated flame retardants), personal care products and intravenous tubing (e.g., phthalates), antimicrobials (e.g., triclosan), and textiles and clothing (e.g., perfluorochemicals). Endocrine disrupters can bind to hormone receptors, compete with endogenous hormones for receptor binding, stimulate or inhibit intracellular signaling mechanisms, alter gene expression, and affect epigenetic functions. Environmental chemical exposure effects are more severe during developmental periods and can be transgenerational. Given the impact on health broadly and reproductive health specifically, reproductive health providers need to understand the risks of environmental toxicants, their effects on reproductive capacity and outcomes, and ways to mitigate these effects, including advocacy for regulatory changes.

Keywords

Reproductive environmental health
pregnancy
prenatal
reproduction
environment
toxin
endocrine disruption
bisphenol A
phenol
phthalate
polyvinyl chloride
perfluorinated compound
pesticide
toxic chemicals
flame retardants

and UK reproductive health professional societies formally recognized the opportunity to advance women's health by championing the prevention of patient exposure to toxic environmental chemicals.[13-15] In 2015, reproductive health professionals around the world issued a call to action on reproductive environmental health and established a structure to ensure clinical engagement to advance this topic among health practitioners and policy makers (see Recommended Online Resources 1 through 5).[16,28] Today, reproductive health professionals around the world have moved from awareness toward action on preventing exposure to environmental chemicals.[29]

Key Scientific Concepts

- *Preconception and prenatal exposure to environmental chemicals can impact the health of the pregnancy and the child, as well as adult health and the health of future generations.*
- *The fetus can be uniquely sensitive to even small amounts of environmental chemicals.*
- *Intergenerational harm can result from in utero exposure to exogenous chemicals.*
- *The placenta does not protect the fetus from many damaging chemicals, and fetal exposure can be higher than maternal exposure.*

Several key scientific concepts underlie current understanding of reproductive environmental health.

Developmental Origins of Adult Health and Disease

The concept of developmental origins of adult health and disease describes links between the in utero environment, the external environment, an individual's genes, and the propensity to develop disease or dysfunction later in life.[17] The central nervous system, cardiovascular system, various endocrine systems, and the immune system are particularly vulnerable to adverse effects during development, and neurodevelopmental disorders and some cancers may well be initiated before birth or during early postnatal life.[19]

The Fetus Can Be Uniquely Sensitive to Chemical Exposures: Thalidomide and Other Agents of Concern

The embryo, fetus, and developing human are highly vulnerable to exposure from even small amounts of environmental toxicants. This vulnerability is due to the unique and rapidly changing physiology, growth, and development of humans (i.e., high mitotic indices and cellular differentiation in developing organs; high metabolic rate; and an underdeveloped immune system, blood-brain barrier, and liver detoxifying mechanism).[30]

A critical window of susceptibility occurs when exposures to environmental contaminants can disrupt or interfere with the physiology of a targeted cell, tissue, or organ[19]; exposures that occur during this time can lead to permanent and lifelong health effects and can be transmitted to subsequent generations. Sensitive windows of susceptibility can still permit the development of disease but with less intensity and severity as compared with those occurring in the critical window.[31] Critical and sensitive windows occur during times of rapid development and cellular differentiation and proliferation such as those that occur during gametogenesis, embryogenesis, implantation, pregnancy, infancy, childhood, puberty, and lactation.

In the 1960s, the drug thalidomide was given to pregnant women to prevent morning sickness. While women who took the drug did not experience ill health effects, their children experienced a high rate of congenital limb and gastrointestinal malformations, particularly when their mother took the drug during the period of the 28th through the 42nd day after conception, which is the critical period of limb development.[32] More than 10,000 children in 46 countries that approved the drug were born with deformities as a consequence of their mothers being prescribed the drug during pregnancy.[33]

Intergenerational Harm Can Result From In Utero Exposure to Exogenous Chemicals: Diethylstilbestrol

Environmental chemical exposures can affect first generation (F0 [parental]) and second generation (F1 [offspring] and F2, germ cells of offspring) (Fig. 19.1). To determine whether alterations are transmitted transgenerationally, the F3 generation must be studied.[34]

Adverse health impacts of in utero exposure to environmental chemicals may appear at birth, such as with thalidomide, and may also be delayed and/or manifest in future generations. This latter outcome is exemplified by the pharmaceutical diethylstilbestrol (DES), an estrogen that was prescribed in up to 10 million pregnancies from 1938 to 1971 to prevent miscarriage with no immediate adverse health impacts for the mother or child being observed. Reproductive tract abnormalities began to emerge in the daughters and sons of DES-exposed women only at puberty, and they continued to emerge 40 years after the index pregnancies and long after its use ended. Delayed health impacts of in utero exposure to DES include clear cell adenocarcinoma of the vagina and cervix, structural reproductive tract anomalies, infertility, poor pregnancy outcomes, and breast cancer among the daughters of women who took DES,[35] and hypospadias among their sons and grandsons.[36] This is a remarkable example of transgenerational inheritance, and mechanisms specifically underlying this process are unclear.

The Placenta Does Not Protect the Fetus From Many Damaging Environmental Chemicals: Methyl Mercury

Environmental chemicals can cross the placenta, and in some cases, such as with methyl mercury, they can bioaccumulate such that the fetal exposure is higher than maternal exposure. In the 1950s, waste discharge from a chemical factory in Japan polluted Minamata Bay, a primary source of food for the local population. Pregnant women who consumed contaminated fish and shellfish from the Bay were exposed to methyl mercury and subsequently gave birth to children with severe neurologic deficits, comprising a syndrome named *Minamata disease*. This tragedy established that the placenta does not protect the fetus from exposure to exogenous chemicals. Subsequent research has documented that developmental and cognitive effects can occur in children

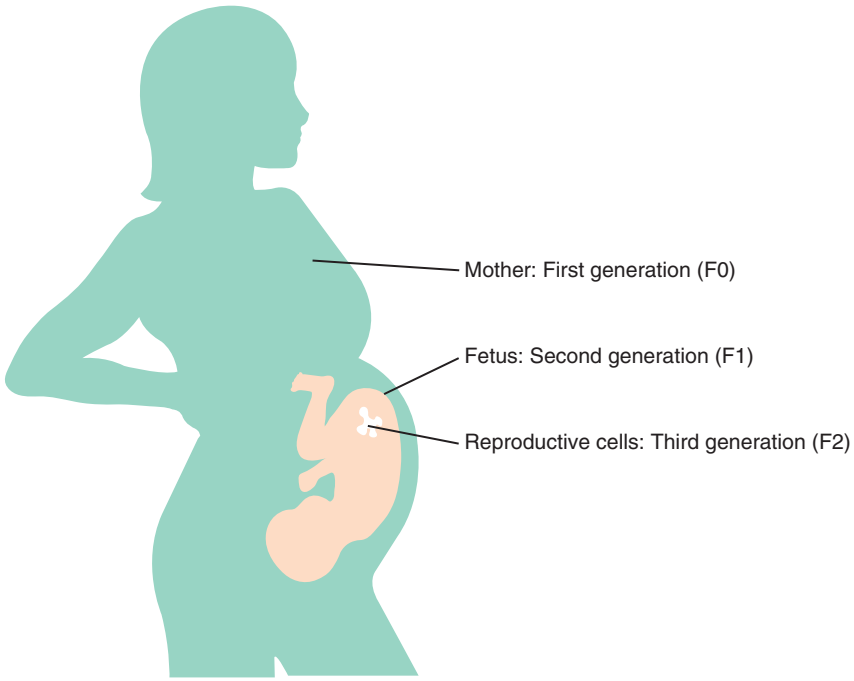

FIGURE 19.1 Three generations are exposed to environmental conditions (e.g., diet, stress, toxicants, and hormones). To provide a convincing case for epigenetic inheritance, an epigenetic change must be observed in the fourth generation. *(Modified with permission from Perera F, Herbstman J: Prenatal environmental exposures, epigenetics, and disease.* Reprod Toxicol *31:363–373, 2011.)*

exposed prenatally to mercury even at low doses that do not result in effects in the mother and that the adverse neurologic effects of methyl mercury exposure may also be delayed.[37]

Human Exposure to Environmental Chemicals

- *Every day, everyone, everywhere is exposed to industrial chemicals.*
- *Exposures and risks are inequitably and unequally distributed.*

Synthetic Chemicals and Heavy Metals Are Ubiquitous in the Environment

Chemicals in the environment are manufactured for various uses (e.g., synthetic chemicals for consumer and industrial applications); they are also by-products of industrial and human activity, and they are released through mining (e.g., heavy metals such as lead and mercury). Tens of thousands of chemicals circulate in global commerce, with over 4800 chemicals imported or manufactured in excess of 1 million pounds each per year.[38] In the United States alone, chemicals in commerce increased more than 15-fold over the past 70 years;[39] in 2012, 9.5 trillion pounds of industrial chemicals were domestically manufactured and imported into the United States,[40] which is the equivalent of 30,000 pounds for every US resident. The vast majority of chemicals in commerce have not been fully tested for reproductive, developmental, or other health effects.[41,42]

The thousands of high-volume chemicals in commerce are ubiquitous in the environment, which poses a major challenge to establishing health impacts and implementing effective interventions. Presented in the following are classes of chemicals and metals illustrative of the most widespread environmental chemicals. Table 19.1 presents where these chemicals and other common chemicals are found and specific health outcomes associated with exposure.

- **Persistent organic pollutants (POPs):** These include chemicals such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) that do not break down in the environment. While certain POPs such as the pesticide dichlorodiphenyl-trichloro-ethane (DDT), its metabolite dichlorodiphenyldichloroethylene (DDE), and PCBs have been banned in the United States for decades, they are still found in virtually the entire population due to their ubiquitous presence in the environment and long half-life and lipid solubility.[43]
- **Pseudo-persistent compounds:** These compounds can be metabolized and removed from the body, but because exposure is consistent, they are found in most human samples. Examples include phthalates, polycyclic aromatic hydrocarbons (PAHs), perfluorochemicals (PFCs), bisphenol A (BPA), and perchlorate.[43,44]
- **Metals**: Metals commonly found in the environment include mercury, arsenic, and lead. Due to public policy initiatives that removed lead from gasoline, paint, food cans, and other products, blood levels of lead have dropped precipitously in the United States.[8] However, the 2015 discovery of lead in Flint, Michigan's drinking water reveals that there remain populations within the United States with high blood lead levels, which are often caused by exposure to lead-contaminated paint and lead in water pipes.[45,46]

Table 19.1 Examples of Exposure Sources and Pathways and Selected Health Impacts of Preconception Exposure to Environmental Contaminants

Chemical	Exposure Sources and Pathways	Selected Health Impact (Reproduction, Poor Birth Outcome, Neurodevelopment, and Cancer)
PCBs	Used as industrial insulators and lubricants; banned in the 1970s, but persistent in the aquatic and terrestrial food chains, which results in exposure by ingestion.	• Decreased semen quality • Low birth weight • Development of attention deficit-hyperactivity disorder–associated behavior • Reduced intelligence quotient
PFAS	Widely used man-made organofluorine compounds with many diverse industrial and consumer product applications; examples are PFOS and PFOA, which are used in the manufacture of nonstick Teflon and other trademark cookware products and in food-contact packaging to provide grease, oil, and water resistance to plates, food containers, bags, and wraps that come into contact with food; persist in the environment; occupational exposure to workers and general population exposure by inhalation, ingestion, and dermal contact.	• Pregnancy-induced hypertension and preeclampsia • Reduced birthweight • Reduced fetal growth • Increased risk for thyroid disease in children
PBDEs	Flame retardants that persist and bioaccumulate in the environment; they are found in furniture, textiles, carpeting, electronics and plastics that are mixed into, but not bound to, foam or plastic.	• Impaired neurodevelopment • Reduction in sustained attention and fine manipulative abilities
Phenols	Examples are BPA, triclosan, and parabens. BPA: Chemical intermediate for polycarbonate plastic and resins; found in consumer products and packaging; exposure through inhalation, ingestion, and dermal absorption. Triclosan: Synthetic chlorinated aromatic compound with antibacterial properties; used in many consumer products such as antibacterial soaps, deodorants, toothpastes, cosmetics, fabrics, plastics, and other products; exposure is through ingestion, dermal contact, and consumption of contaminated food and drinking water. Parabens: Most commonly used preservatives in cosmetic products, including makeup, moisturizers, hair care products, and shaving products; also used in foods and drugs; exposure through dermal absorption and ingestion.	• Female reproductive toxicity (e.g., recurrent miscarriage) • Aggression and hyperactivity in female children • Impaired behavioral regulation (anxious, depressive, and hyperactive behaviors) in girls aged 3 years • Reduced neonatal TSH in boys • Decreased thyroxine concentrations* • Found to have estrogenic activity in vitro but further studies needed for their reproductive and developmental health impacts
Phthalates	Synthetically derived; used in a variety of consumer goods such as medical devices, cleaning and building materials, personal care products, cosmetics, pharmaceuticals, food processing, and toys; exposure occurs through ingestion, inhalation, and dermal absorption.	• Shortened gestational age • Male reproductive tract development (reduced anogenital distance) • Impaired neurodevelopment • Reduction in executive function at age 4–9 years
Heavy metals	Cadmium: Used in batteries, pigments, metal coatings, and plastics; for nonsmoking public, exposures mainly occur through diet (shellfish, organ meats, grains such as rice and wheat, leafy vegetables, and some root crops such as potato, carrot, and celeriac); for smokers, exposure mainly occur through tobacco smoke. Lead: Occupational exposure occurs in battery manufacturing/recycling, smelting, car repair, welding, soldering, firearm cleaning/shooting, stained-glass ornament/jewelry making; nonoccupational exposure occurs in older homes where lead based paints were used, in or on some toys/children's jewelry, water pipes, imported ceramics/pottery, herbal remedies, traditional cosmetics, hair dyes, contaminated soil, toys, costume jewelry. Mercury: Coal-fired power plants are largest source in the United States; primary human exposure is by consumption of contaminated seafood.	• Alterations of epigenetic signatures in the DNA (DNA methylation) of the placenta and of the newborns • Reduced IQ • Increased risk of emotional problems in 7–8-year-old boys • Alterations in genomic methylation • Impaired neurodevelopment (decrease in cognitive function, decreased intelligence quotient, increased incidence of attention-related behaviors and antisocial behavior problems, and decreased hearing measured in children, reduced intellectual development) • Reduced cognitive performance • Impaired neurodevelopment • Reduced psychomotor outcomes • Neurobehavioral deficits
Perchlorate	Used to produce rocket fuel, fireworks, flares, and explosives and can also be present in bleach and in some fertilizers; primary pathway for exposure is through drinking water caused by contaminated runoff.	• Altered thyroid function in newborns

Table 19.1 Examples of Exposure Sources and Pathways and Selected Health Impacts of Preconception Exposure to Environmental Contaminants—cont'd

Chemical	Exposure Sources and Pathways	Selected Health Impact (Reproduction, Poor Birth Outcome, Neurodevelopment, and Cancer)
Pesticides	Applied in large quantities in agricultural, community, and household settings; in 2007, >1.1 billion pounds of active ingredients were used in the United States; it can be ingested, inhaled, and absorbed by the skin; pathways of exposure include food, water, air, dust, and soil.	• Impaired fetal growth • Impaired cognitive development • Impaired neurodevelopment: increased risk of pervasive developmental disorder at age 2 years, increase in attention problems and attention deficit hyperactivity disorder behaviors at age 3 years and reduction in working memory capabilities and IQ at age 7 years • Increased susceptibility to testicular cancer • Childhood cancers (leukemia and brain tumor)
Solvents	Liquids or gases that can dissolve or extract other substances; they are used in manufacturing, service industries such as dry cleaning and printing, and consumer products including stain removers, paint thinners, nail polish removers, and hobby/craft products; examples are benzene, gasoline, ethyl alcohol, methanol, phenol, styrene, toluene, trichloroethylene, and xylene; exposure occurs through inhalation, dermal absorption, and ingestion.	• Spontaneous abortion and fetal loss • Decreased fetal and birth weight • Congenital malformations

*Based on animal studies.
BPA, Bisphenol A; *PBDEs*, polybrominated diphenyl ethers; *PCBs*, polychlorinated biphenyls; *PFAS*, perfluoroalkyl substances; *PFOA*, perfluorooctanoic acid; *PFOS*, perfluorooctane sulfonate; *TSH*, thyroid-stimulating hormone.
Reprinted with permission from Wang A, Padula A, Sirota M, Woodruff TJ: Environmental influences on reproductive health: the importance of chemical exposures. *Fertil Steril* 106(4):905–929, 2016. Table 19.1. Table references can be found in Wang et al.

Environmental Chemicals in Pregnant Women

Environmental chemicals permeate the air, water, food, and consumer products; consequently, exposure to environmental chemicals among pregnant women in the United States[47] and around the world[16,48] is ubiquitous. A report by the US National Cancer Institute concluded that "to a disturbing extent babies are born 'pre-polluted'."[21] In population-based surveys of pregnant women in the United States, specific PCBs, organochlorine pesticides, PFCs, phenols, PBDEs, phthalates, PAHs, and perchlorate were detected in 99% to 100% of pregnant women.[47] Many chemicals were measured at levels similar to the levels encountered in epidemiologic studies that demonstrated adverse reproductive and developmental outcomes. Furthermore, virtually all women were exposed to multiple chemicals. Exposure to multiple chemicals that impact the same health endpoint (e.g., brain development) can result in a greater risk than by exposure to a single chemical alone.[49]

Fetal Exposure to Environmental Chemicals

As exemplified by the Minamata disaster described previously, placental transfer of chemicals is now well established. Fetal exposure varies depending on the chemical structure and composition, with some chemicals having higher or lower affinity for transplacental transfer.[50,51] For example, measured concentrations of 87 environmental pollutants in mother-child samples demonstrated that all substances found in the mothers were also present in fetal tissues and cord blood; however, the degree of transplacental passage and correlation with maternal levels varied depending on chemical structure, lipid solubility, and molecular weight.[52] Recent research suggests that fetal exposure exceeds maternal exposures not just for methyl mercury but also for many other environmental chemicals.[53]

Exposure and Risks Are Inequitably and Unequally Distributed

Exposure to toxic environmental chemicals and associated adverse health outcomes are inequitably and unequally distributed among people, communities, and countries. Some of these differences in vulnerabilities and risk relate to age, sex, genes, underlying health status, and coexposure to other environmental stressors.[49,54] Other vulnerabilities are related to socioeconomic status, occupation, and/or racial discrimination and other social factors that increase stress.[55] For example, people with low incomes bear a disproportionate burden of morbidity and mortality, loss of family income and productivity, and environmental degradation related to environmental exposures[56]; indigenous peoples in Canada, the United States, and other countries incur a higher burden of toxic exposures and resulting adverse health outcomes.[57,58] Many of these factors can predispose the population to be more sensitive to the effects of chemical exposures and multiple vulnerabilities increasing that sensitivity. Thus environmental chemicals may be an important factor in health disparities.[59] Furthermore, as these differences mediate risk, the National Academy of Sciences has recommended that in the absence of evidence to the contrary, any level of exposure should be assumed to be potentially harmful (i.e., there is no assumption of a "safe dose").[54]

Mechanisms

- *Exposure to endocrine disrupting chemicals can adversely impact reproductive success by interfering with any aspect of hormone action.*
- *Epigenetic modifications affect gene expression, cell and tissue function, and disease risk.*
- *Through epigenetic mechanisms, environmental chemicals, including but not limited to endocrine disrupting chemicals, can impact reproductive success and other aspects of healthy human development across generations.*

Endocrine Disruption

EDCs can modify multiple biological processes by interfering with any aspect of hormone action, and thus these chemicals have the potential to affect steroid hormone-dependent human reproductive tract development and adult reproductive function. Exposure to DES and other chemicals (see later) are a testimony to these interferences. In addition to being reproductive "disrupters," EDCs have recently been implicated as thyroid disrupters, neurodevelopmental disrupters, obesogens, and diabetogens,[18] which directly and indirectly affect reproductive success.

The question arises, through what mechanisms do EDCs affect such a diverse set of functions and processes? It is not surprising that they are mediated by multiple mechanisms. For example, specific hydrophobic EDCs in cigarette smoke, plasticizers, pesticides, cosmetics, and dietary components interact with estrogen receptors (ER) α and β, bind to estrogen response elements (EREs), and activate or repress gene expression via genomic pathways. In addition, they can evoke rapid responses involving membrane-associated ERs and affect nongenomic pathways, including kinase signaling cascades, as well as binding and blocking androgen action at the androgen receptor (AR).[18,60] Some EDCs can also bind to the aryl hydrocarbon receptor (AHR), associate with AHR nuclear translocator (ARNT), and bind to dioxin response elements (DREs).[60] EDCs can also change cellular processes by activating ion channels, inducing proinflammatory cytokines and chemokines, promoting oxidative stress, and altering cell proliferation and differentiation. In addition, EDCs can act via nonsteroid hormone receptors (e.g., GPR30, peroxisome proliferator-activated receptor [PPAR], and the thyroid receptor ThR)[18] and affect enzyme activities and organ patterning.[60]

Epigenetic Mechanisms

Increasing evidence suggests that epigenetic mechanisms underlie tissue and organ dysfunction due to some EDCs, including DNA methylation, histone modifications, and microRNA (miRNA) expression and subsequent gene expression.[61] In vitro studies with human and rodent cell lines and in vivo data in rodents and humans reveal effects of environmental chemicals, including EDCs, on global and gene promoter-specific DNA methylation. For example, arsenic and cadmium as well as DES and benzene affect genome-wide DNA methylation and promoter methylation regulating *p53*, *p15*, and the *Agouti* gene expression.[62] Maternal smoking affects genome-wide promoter regions of the human placenta (14,000 genes), as well as specific genes (e.g., *LINE1* and *AluYb8*) in the placenta.[63] Histone acetylation, dimethylation, trimethylation, and monoubiquitination modifications have been observed with heavy metals, and multiple miRNAs, including tumor suppressing and oncogenic miRNAs[62] and placental miRNA changes associated with maternal smoking.[63] These modifications in turn affect gene expression, cell and tissue function, and disease risk. Importantly, the impact of EDCs can be significant for reproductive success across generations, especially considering the methylation/demethylation changes that occur normally during gametogenesis and embryogenesis (Fig. 19.2).[34] Environmental modifications of gene expression can affect embryonic imprinting, cellular differentiation, and phenotypic expression[64] that can have F0, F1, F2, and F3 generational impacts.

Reproductive Health Outcomes Linked to Environmental Chemical Exposures

- *Prenatal exposure to environmental chemicals commonly found in our air, water, food, and consumer products are linked to myriad adverse reproductive health outcomes.*
- *Exposure to endocrine disrupting chemicals may significantly impact both female and male reproductive capacity.*
- *Adverse reproductive health outcomes linked to exposure to environmental chemicals include fertility and fecundity, pregnancy, and neonatal and child health outcomes.*

The literature demonstrating links between environmental chemical exposures and adverse reproductive outcomes has grown substantially over the past several decades. Prenatal exposure to environmental chemicals has been linked to a diverse range of health impacts across the lifespan of individuals, including, but not limited to, harm to healthy human reproduction, poor birth outcomes, neurodevelopmental problems, and cancer. Table 19.1 presents examples of adverse health impacts of prenatal exposure to chemicals found commonly in our air, water, food, and/or consumer products.

Studies in mice, rats, hamsters, lamb, sheep, and humans reveal that EDCs may significantly impact female reproductive capacity, including ovarian steroidogenesis, oocyte quality, menopause timing, age of puberty, and reproductive disorders (see Chapter 8).[18,65-71] Fig. 19.3 pictorially demonstrates disruption at nearly every stage of ovarian follicle development and each stage of steroidogenesis.[18,72] Similar disruption in the male occurs, for example, with prenatal exposure to some EDCs (mostly antiandrogens, estrogens, and dioxins) and increased risk of cryptorchidism, hypospadias, abnormal fetal and adult Leydig cell and Sertoli cell steroidogenesis, sperm quality, and testicular (germ cell) cancer. Fig. 19.4 illustrates the testicular dysgenesis syndrome (TDS) proposed by Skakebaak (2003) in which spermatogenesis, undescended testis, and hypospadias as well as testicular (germ cell) cancer are part of a spectrum of male reproductive tract dysfunction due in part to EDCs. These syndromes range in severity from mild, to medium, to severe TDS, and they can have transgenerational impact.[73]

Examples of the range of potential health impacts are outlined in the following.

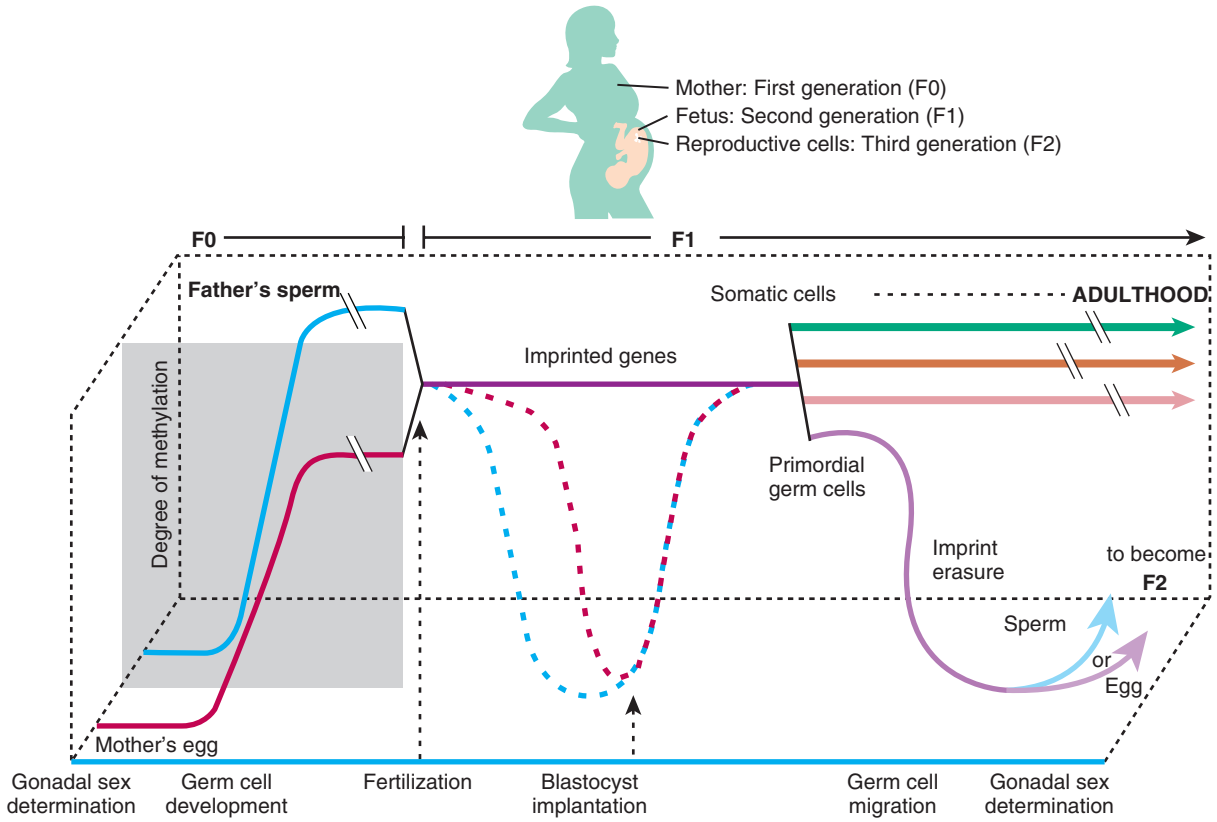

FIGURE 19.2 Multiple periods when environmental exposures can affect first-generation (F0 [parental]) and second-generation (F1 [offspring] and F2, germ cells of offspring). DNA methylation status potentially affecting phenotype. To demonstrate whether epigenetic alterations are transmitted transgenerationally, the F3 generation must be studied. *(Data from Perera F, Herbstman J: Prenatal environmental exposures, epigenetics, and disease.* Reprod Toxicol *31:363–373, 2011, with permission.)*

Fertility and Fecundity

A number of common environmental exposures have been associated with impairments in fertility or fecundity for both men and women, including air pollution, POPs, PFCs, BPA, pesticides, and lead.[18,61] Disruption of any one of the many steps during ovulation, fertilization, and implantation has the potential to cause infertility or to impair fecundity. For example:

- **POPs** such as PCBs, dioxins, and furans mimic estrogen and are implicated in the origins of endometriosis in animal models.[18] Endometriosis has also been associated with exposure to other chemicals that disrupt hormone function.[74,75] For example, there is an increased risk of endometriosis in women who were regularly fed soy formula as infants.[76]
- **BPA**, used in many common consumer goods such as water bottles, sports equipment, thermal paper receipts, and food packaging, is a female and male reproductive toxicant.[77] In females, there is strong evidence that BPA disrupts ovarian and uterine endocrine function.[77] In males, high levels of exposure are associated with sexual dysfunction, including reduced frequency of intercourse, increased ejaculatory dysfunction, reduced satisfaction with their sex life, reduced sex drive, and reduced ability to have an erection.[78]
- **Pesticides** have long been implicated in a wide range of adverse reproductive outcomes. In the 1970s, use of the pesticide dibromochloropropane (DBCP) led to infertility in a cohort of occupationally exposed men.[79] The scope of pesticides' potential to disrupt endocrine systems is broad and has been reviewed elsewhere.[80]
- **Lead** exposure (at blood lead over 40 to 50 µg/dL) impairs fertility in men and women. In men, higher lead levels are toxic to sperm. In women, higher levels are associated with increased risk of spontaneous abortion and stillbirths; while these adverse health consequences are documented at higher levels of exposure, CDC has found that "no measureable level of blood lead is known to be without deleterious effects."[81,82]

Pregnancy, Neonatal, and Child Outcomes

Many environmental chemicals for which exposure is prevalent are linked to adverse pregnancy, neonatal, and associated children's health outcomes. A 2016 consensus statement by leading scientists, health professionals, and child health advocates lists prime examples of toxic chemicals in the everyday environment that can contribute to learning, behavioral, or intellectual impairment, including neurodevelopmental disorders such as ADHD and autism.[20] The chemicals implicated include phthalates, pesticides, lead, flame retardants, mercury, and multiple common air pollutants. Additional examples of adverse fetal and child health outcomes from some of these same chemicals and others include the following:

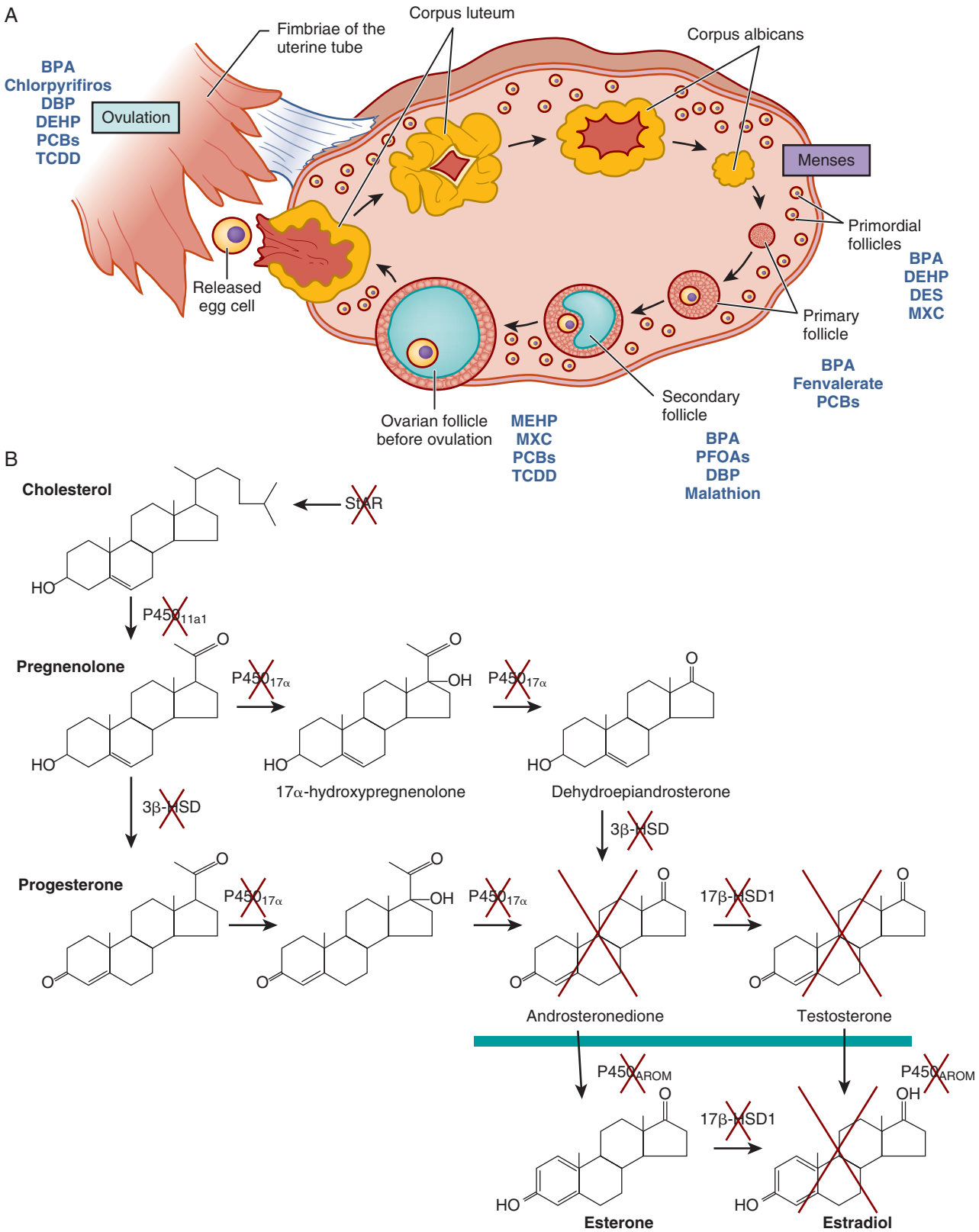

FIGURE 19.3 Endocrine disrupting chemicals disrupt prenatal and postnatal ovarian development, egg quality, (*insert*, A) and steroidogenesis (*insert*, B). *Red Xs* indicate potential areas of endocrine disruption. *BPA*, Bisphenol A; *DBP*, dibutyl phthalate; *DEHP*, di(2-ethylhexyl)phthalate; *DES*, diethylstilbestrol; *MEHP*, mono(2-ethylhexyl)phthalate; *MXC*, methoxychlor; *PCBs*, polychlorinated biphenyls; *PFOA*, perfluorooctanoic acid; *TCDD*, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. *(Modified with permission from Gore AC, Chappell VA, Fenton SE, et al: EDC-2: The Endocrine Society's second scientific statement on endocrine-disrupting chemicals.* Endocr Rev *36:E1–E150, 2015. Disruption data also from Kwitkiewicz, 2010; Xu, 2010; Mok-lin, 2010; Luderer, 2013; Erlich, 2014; Grindel, 2015.)*

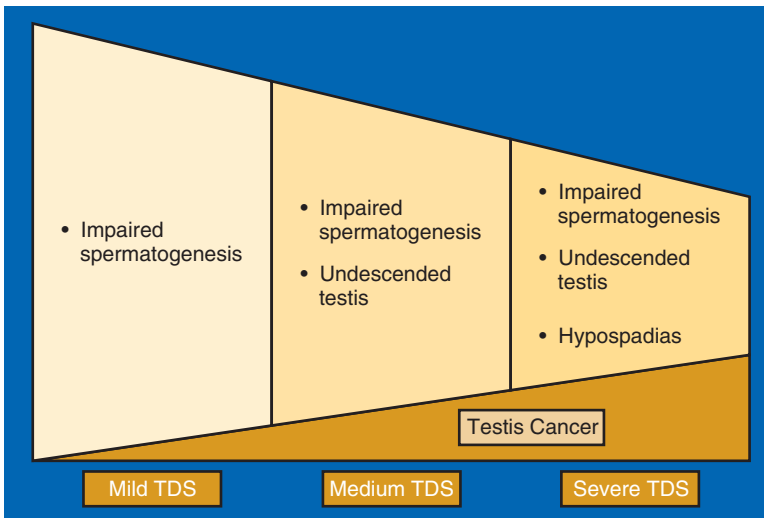

FIGURE 19.4 Testicular dysgenesis syndrome. *(Modified with permission from Skakkebæk NE, Rajpert-De Meyts E, Main KM: Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects.* Hum Reprod *16:972–978, 2001.)*

- **Phthalates** (used to make plastics softer and more pliable and used as fragrances in personal care products) are associated with antiandrogenic adverse effects on the male reproductive tract (i.e., reduced anogenital distance) in animal models and in prospective human studies.[83-85] They are also associated with adverse behavioral outcomes in children[86,87] and hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, eclampsia, or the HELLP syndrome of hemolysis, elevated liver enzymes, and low platelet count.[88]
- **Perfluorooctanoic acid (PFOA)** (used for making nonstick cookware and stain and water-resistant consumer goods and food packaging) is known to be toxic to reproductive health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.[89]
- **Lead** impacts child cognitive function, and its adverse health impacts also extend to cardiovascular, immunologic, and endocrine effects.[81]
- **PBDEs** are a class of chemicals used extensively as flame retardants in foam, electronics, and plastics, and thus these chemicals are found in finished products such as furniture, textiles, carpets, and electronic devices. Higher levels of PBDEs are associated with adverse pregnancy outcomes[90] and with a significant decrease in birth weight.[91]

Evidence-Based Decision Making in Environmental Health

- *The context for decision making about environmental chemicals is different than other clinical decisions; patients are exposed to many and varied biologically active substances that have not been adequately scrutinized for safety; "treatment" decisions are about whether to let such exposures persist.*
- *Experimental human evidence is generally unavailable for decision making in environmental health; decisions rest largely on experimental animal and observational human studies.*
- *As exposure is already occurring, delays in decision making about environmental chemicals come with adverse health consequences.*
- *To advance timely decision making about environmental exposures, systematic review methods that incorporate the decision context and evidence stream in environmental health are rapidly gaining traction.*

Decision Context in Environmental Health

The context for decision making differs between the disciplines of environmental health and clinical health sciences. Pharmaceuticals evaluated for clinical use are subjected to premarket testing for efficacy and safety and are prescribed based on balancing the benefits and risks to patient health. On the other hand, due to shortcomings of the regulatory process for environmental chemicals, industrial chemicals generally do not receive comparable scrutiny. Putative benefits are largely unrelated to patient health, and exposures are generally unintentional and highly variable. In practice, most individuals are exposed without awareness of their exposure or of credible scientific information on reproductive, developmental, and other toxicities. This state of affairs has been described by Dr. Linda Birnbaum, the Director of the US National Institute of Environmental Health Sciences and the National Toxicology Program, as allowing environmental chemicals to act as "uncontrolled medicines"[92] and by Carl Cranor, a philosopher at the University of California, Riverside, as allowing people to be "legally poisoned."[93]

Evidence Stream in Environmental Health

Current decision making in environmental health rests on animal and epidemiologic data, and wildlife studies can further strengthen evidence supporting clinical practice guidelines. In contrast to the clinical sciences, experimental human evidence is largely unavailable for decision making regarding environmental hazards, as randomized controlled trials are precluded by ethical considerations. Research has shown there is concordance of developmental and reproductive effects between animal and human studies, and animal studies are currently recognized as reliable predictors of human health effects.[94] Recent legislation encourages decreased use of

Table 19.2 Examples of Systematic Reviews in Environmental Health

Study Question	Conclusion	References
Does developmental exposure to PFOA affect fetal growth in humans?	PFOA is "known to be toxic" based on "sufficient" evidence of toxicity for the human and the nonhuman evidence.	89
Is there an association between fetal growth and maternal GFR in humans?	The association between fetal growth and GFR is "not classifiable" based on "inadequate" human evidence.	99
Does exposure to triclosan have adverse effects on human development or reproduction?	Triclosan is "possibly toxic" to reproductive and developmental health based on "sufficient" nonhuman evidence and "inadequate" human evidence of an association between triclosan exposure and thyroxine concentrations.	100
Does developmental exposure to PBDEs in humans affect (1) quantitative measures of intelligence, or (2) ADHD and attention-related behavioral conditions?	There is "sufficient" evidence of an association between prenatal PBDE exposure and decrements in intelligence and "limited" evidence for ADHD and attention-related behaviors.	101
Is developmental exposure to air pollution associated with ASD?	There is "limited evidence of toxicity" for the association between early life exposure to air pollution as a whole and diagnosis of ASD. The strongest evidence was between prenatal exposure to particulate matter and ASD.	102
Is exposure to formaldehyde associated with asthma?	There is "sufficient evidence" of an association between formaldehyde exposure and asthma.	103

ADHD, Attention-deficit/hyperactivity disorder; *ASD*, autism spectrum disorder; *GFR*, glomerular filtration rate; *PBDE*, polybrominated diphenyl ether; *PFOA*, perfluoroocatnoic acid.

animal models and calls for increased reliance on in vitro screening and testing.[95] While reducing animal research is a laudable goal, this approach currently has limited capacity to predict health outcomes in humans, particularly for the wide range of susceptibilities in the population due to age, disease status, genetic variability, and socioeconomic and other variables. Epidemiologic studies provide the most direct link between an environmental exposure and increased risk of adverse human health outcomes; however, it can take decades for the health impacts of a given exposure to be manifest. By the time human evidence is available, the opportunity for timely prevention has mostly been lost.

Need for Timely Decision Making in Environmental Health

Over a half-century of lessons in the regulation of toxic chemicals underscores how the health impact of toxic chemicals expands over time.[96,97] More populations are exposed, and more adverse health impacts are documented. "Safe" limits become lower over time. Thus timely decision making based on the evidence at hand is critical as delays in decision making come with adverse health consequences for individuals, populations, and future generations. To advance timely evidence-based decision making, systematic review methods applicable to environmental health's decision context and evidence stream have been developed.[98] Table 19.2 presents the findings of six "proof-of-concept" case studies that apply systematic review methods to synthesize the evidence linking environmental chemical exposure to health. Systematic review methods are rapidly gaining traction in the field of environmental health,[104,105] and it is anticipated that clinical decision making will increasingly be informed by their use in the future.

Clinical Management

- *Reducing or eliminating exposure to environmental contaminants prior to conception is the most effective strategy for preventing adverse health impacts.*
- *Reproductive and other health professionals do not need to become topic experts in order to play a critical role in preventing adverse health outcomes.*
- *Clinicians should take an exposure history and provide patients with resources and referrals.*
- *Numerous government and academic resources and referrals about specific environmental exposures and reproduction are available to assist in clinical management.*

Reducing or eliminating exposure to environmental contaminants prior to conception is the most effective strategy for preventing adverse health consequences. At the same time, pregnancy is an opportunity to teach the public, as patients who are pregnant and couples planning a family are often highly motivated to learn about chemical exposures that might impact the health of their child.

Physicians and other reproductive health professionals should be educated about the potential impact of environmental exposures on reproductive health so that they are prepared to answer their patients' basic questions. Also, providers need to be aware of resources and referral mechanisms to which they can direct challenging inquiries. Links to clinician resources, including patient-centered brochures, web links, and referral mechanisms, are provided in the resources section. Clinicians do not need to become experts in environmental and occupational health to fulfill this crucial role.[106] For example, clinicians can provide science-based information and discuss areas of uncertainty about environmental chemicals so that patients can make informed choices based on their values and preferences.

Taking an Exposure History

Taking an exposure history is a key first step. Examples of exposure history forms are available at http://prhe.ucsf.edu/clinical-practice-resources. When counseling patients about their exposures, clinicians need to:

- Understand patient risk is a function of the toxicity, dose, frequency, duration, and timing of the exposure, and individual patient vulnerability, including any underlying

health conditions. Routes of exposure include transdermal, inhalation, and ingestion.

- Advise patients on how to prevent exposures at home, work, and in the community.
- Recognize that socioeconomic and racial disparities can exacerbate the amount of environmental exposures experienced by an individual and that understanding the environment of the patient population can help target high-risk exposures.
- Identify patients with hazardous occupations or hobbies. Women and men of reproductive age with occupational exposures to substances with reproductive and developmental toxicity are at high risk and susceptible to adverse reproductive outcomes.[107] Legal workplace limits are not created to protect pregnant women.[107,108] Although women who are exposed to chemicals through hobbies may have lower exposures than those women who are employed in similar industries (e.g., jewelry making), they may have less training in safety.
- Recognize that many recommendations can be implemented at little to no cost—for example: washing hands before eating, taking shoes off before entering a house, damp mopping regularly for dust control, using cast iron pans for cooking instead of nonstick pans, avoiding the use of pesticides, choosing fish that are low in mercury, and avoiding: eating processed foods, microwaving foods in plastic, wearing cosmetics with fragrances, and handling cash register receipts now ubiquitously containing BPA. There is a small but growing literature assessing lifestyle interventions, and these studies have generally shown that such interventions can decrease exposure to or body burdens of specific toxins.[109-112]

Research has revealed two main themes in obstetricians' hesitancy to address issues of environmental exposures with patients: (1) "bigger fish to fry"—namely, that other clinical or health concerns are of higher priority than environmental concerns; (2) "Pandora's box"—the idea that broaching the subject of environmental concerns leaves obstetricians open to a barrage of questions to which they do not have answers.[113] Additional issues of competing clinical priorities, time limitations, and the current gaps in the evidence base are also barriers to counseling women effectively. Complementary approaches that require minimal time on the part of the busy clinician include (1) having ancillary staff place brochures in packets given to patients on entry to prenatal care and/or making brochures available in the waiting or exam rooms; (2) having staff provide patients with information on nutritional counseling or other germane health education regarding avoidance of toxic chemicals.

Referrals and Resources

Health care providers may encounter possible patient exposure issues that they are unable to address adequately due to personal lack of training, knowledge, and/or because the exposure may be significant enough to warrant specialist care or other nonmedical intervention (e.g., a workplace exposure). Table 19.3 presents numerous government and academic entities that provide information about specific environmental exposures of concern, as well as resources

Table 19.3 Resources for Patient Information and Referrals

Resource	Type of Information Available	Available at: Internet/ Telephone
PEHSUs	PEHSUs is a network of physicians trained in environmental health based at academic centers throughout the United States. The PEHSUs provide consultations with pediatric and obstetric experts in environmental health who are poised to respond to questions such as: "Should I tell my patients to avoid manicures in pregnancy?" "I ordered a lead level, and it's high; what should I do?" "Patients are asking me to order hair testing for heavy metals, should I do it?" "My patient is pregnant and renovating an older home; is that a worry?" The PEHSU network also has clinicians available for in-person patient or provider telephone consultation regarding any environmental exposures relevant to pregnancy and childhood. The website has patient and provider factsheets on many topics of interest, including case-based learning eBooks which ground the science of health in stories of fictional people, their families, and communities to enable readers to explore the risk factors for disease and how to prevent disease and promote health and resilience.	http://www.pehsu.net PEHSU-East National Office (Federal Regions 1–5): Tel: (888) 227-1785 (Toll Free) PEHSU-West National Office (Federal Regions 6–10): Tel: (844) PEHSU-W9 or (844) 734-7899 (Toll Free) UCSF/ Western States PEHSU: 1-866-827-3478. http://wspehsu.ucsf.edu/for-clinical-professionals/training/a-story-of-health-a-multi-media-ebook/ Also see Recommended Online Resource 6.
NIOSH	NIOSH has resources and experts who can help find evidence-based answers to patient questions about occupational exposures.	https://www.cdc.gov/cdc-info/ https://www.cdc.gov/niosh/topics/repro/
OSHA	OSHA is a federal agency that sets and enforces federal safety and health standards for the workplace.	(800) 321-6742 or www.osha.gov
ATDSR	ATSDR is a federal public health agency tasked with providing trusted health information to prevent harmful exposures and diseases related to toxic substances.	Toxic Substances Portal: http://www.atsdr.cdc.gov/substances/toxorganlisting.asp?sysid=21
US CDC Guidance on lead in pregnancy	In-depth review of the impact and management of lead exposure in pregnancy. Although lead affects fetuses and children primarily through direct toxic effect, it can also cause endocrine disruption.	http://www.cdc.gov/nceh/lead/publications/LeadandPregnancy2010.pdf

Continued

Table 19.3 Resources for Patient Information and Referrals—cont'd

Resource	Type of Information Available	Available at: Internet/ Telephone
NIH National Library of Medicine Household Products Database	A database of health and safety information regarding household products is searchable by product, ingredients, manufacturer, and health effects; includes information about contents of products, potential health effects, safety and handling.	http://householdproducts.nlm.nih.gov/products.htm
EHP Children's Health	EHP's website features timely children's health research and news as they are published in EHP and links to related material. The page includes a searchable full library of children's health content. The page also includes links to EHP's popular Children's Health Collections; Government resources; Information from and about children's health organizations; Reports of interest; Announcements; and Links to webinars, meetings, and other events related to children's health.	http://ehp.niehs.nih.gov/posting/childrens-health-web-page/
University of California San Francisco's PRHE	PRHE has an extensive website with information specifically for patients and families (available as downloadable brochures) and many resources and links for clinicians and researchers. Information for clinicians includes links to environmental history forms.	http://prhe.ucsf.edu/prhe/families.html Resources for clinicians: http://prhe.ucsf.edu/prhe/clinical_resources.html
SafetyNest	SafetyNest is a one-stop, personalized health education platform designed to transform prenatal care. The app equips health providers and every pregnant woman with a toolkit to reduce diseases linked to toxic chemical exposure.	http://www.mysafetynest.org
TEDX (includes List of Possible Endocrine Disruptors)	The TEDX List of Potential Endocrine Disruptors is a database of nearly 1000 chemicals with the potential to affect endocrine systems. Interactive timeline describes critical windows of development of various organ systems.	http://www.endocrinedisruption.org/ http://www.endocrinedisruption.org/prenatal-origins-of-endocrine-disruption/critical-windows-of-development/timeline-test/
Environmental Working Group (and Skin Deep website)	EWG's website has news and commentary on current environmental issues and consumer information. EWG's Skin Deep is a searchable database of personal care products rated by the toxicity of their ingredients.	http://www.ewg.org/ http://www.ewg.org/skindeep/
CHE	CHE is a nonpartisan organization with a mission to strengthen the science dialogue on environmental factors impacting human health and to facilitate prevention-oriented efforts to address environmental health concerns. Frequent webinars present current research on a variety of topics related to the impact of the environment on health. The website has a searchable database that summarizes links between chemical contaminants and approximately 180 human diseases or conditions. Searches can be made by disease or toxicant.	http://www.healthandenvironment.org/ CHE Toxicant and Disease database http://www.healthandenvironment.org/tddb/

ATDSR, Agency for Toxic Substances and Disease Registry; *CDC*, Centers for Disease Control and Prevention; *CHE*, Collaborative on Health and the Environment; *EHP*, Environmental Health Perspectives; *NIOSH*, National Institute for Occupational Safety and Health; *OSHA*, Occupational Safety and Health Administration; *PEHSUs*, Pediatric Environmental Health Specialty Units; *PRHE*, Program on Reproductive Health and the Environment; *TEDX*, The Endocrine Disruption Exchange.
Modified with permission from Zlatnik MG: Endocrine-disrupting chemicals and reproductive health. *J Midwifery Women's Health* 61(4):442–455, 2016.

for general information about environmental exposures and reproduction.

Health Care System and Public Policy Solutions

- *Society-wide actions to prevent or reduce harmful environmental exposures are essential to patient and population health; individual action alone is not sufficient.*
- *To prevent patient and population exposure to environmental chemicals, reproductive and other health professional societies in the United States and across the globe encourage reproductive health professionals to: (1) Advocate for policies to prevent exposure to toxic chemicals; (2) Work to ensure a healthy food system for all; (3) Make environmental health part of health care; and (4) Champion environmental justice.*

Many environmental exposures cannot be prevented by individual action alone, but rather they require public policy approaches—for example, air and water pollution. There are also many legal, economic, and social justice issues interwoven into the distribution of environmental chemicals throughout our society that cannot be addressed by individual action alone. Furthermore, clinical settings offer limited time for intervention, and by the time a patient arrives for prenatal care, preventable exposures may have already occurred.[16] Thus society-wide actions to prevent exposures are essential to patient and population health. Harnessing the voice of

health professionals to advocate for policies to prevent environmental chemical exposure also offers a powerful way to impact patient health.[29,114,115] To prevent patient and population exposure to toxic chemicals, the International Federation of Gynecology and Obstetrics (FIGO) encourages "prevention measures that support broad-based policy changes in exposure to toxic environmental chemicals that will lead to prevention for all."[16] Specifically, FIGO recommends that obstetricians, gynecologists, midwives, women's health nurse practitioners, nurses, and other health professionals do the following:

1. **Advocate for policies to prevent exposure to toxic chemicals.** In 2016, FIGO submitted comments to the European Commission and to the US Food and Drug Administration in support of stronger regulation of environmental chemicals.[116,117]
2. **Work to ensure a healthy food system for all.** Health care systems are currently leveraging billions of dollars in purchasing power to bring healthier food to diverse and vulnerable populations.[118]
3. **Make environmental health part of health care.** In addition to patient counseling as described previously, global efforts are underway to secure an environmentally sustainable health care sector.[119] For example, health care institutions across the globe are moving toward low-carbon health care delivery and away from fossil fuel based energy development.
4. **Champion environmental justice.** Health professionals working on climate change are championing environmental justice, as its health impacts disproportionately affect low-income and other vulnerable populations.[45,46,120-123]

Conclusion

The science linking the environment to our health has grown substantively since Rachel Carlson's 1962 publication of *Silent Spring*[124] ushered in the field of environmental health. Reproductive health professionals now recognize that preventing exposure to toxic chemicals offers a robust opportunity to keep patients, communities, and future generations healthy. Worldwide, every year, exposure to toxic chemicals results in millions of deaths and costs billions of dollars.[16] In 2016, the World Health Organization calculated that "35% of ischaemic heart disease, the leading cause of deaths and disability worldwide, and about 42% of stroke, the second largest contributor to global mortality, could be prevented by reducing or removing exposure to chemicals such as from ambient air pollution, household air pollution, second-hand smoke and lead."[125] Reducing the disease burden from environmental pollution will also support a broad range of UN Millennium Development Goals of eradicating extreme poverty and hunger, reducing child mortality, improving maternal health, and ensuring environmental sustainability.[125] In the coming years, health professionals will play an increasingly critical role in patient health by intervening in clinical and policy arenas to secure a healthy environment for human reproduction and development.

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Recommended Online Resources

1. 60 Minutes: Toxic Bodies. A series of short videos on environmental health. http://bit.ly/60MiNueTsPlaylist (video).
2. Environmental Exposures and Reproductive Outcomes: A Call to Action! https://www.youtube.com/watch?v=VAtQjhgbPhE (video).
3. Global Reproductive Health and the Environment: What Does the Evidence Say? https://youtu.be/y1BBCLlKsjQ (video).
4. Talking Toxic Chemicals: Global ObGyns Urge Prevention. https://www.youtube.com/watch?v=Pi3WzJzxiQE (video).
5. FIGO 2015: Why are ObGyns Talking Toxins? http://bit.ly/FIGO2015YouTube.
6. A Story of Health: A Multi-media eBook. This free multi-media eBook grounds the science of health in stories of fictional people, their families, and communities to enable readers to explore the risk factors for disease as well as how to prevent disease and promote health and resilience. http://wspehsu.ucsf.edu/for-clinical-professionals/training/a-story-of-health-a-multi-media-ebook/ (ebook).

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