

Reproductive environmental health

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Purpose of review

There is heightened recognition that the environment is an important driver of human reproductive health. This article provides an overview of the nature and extent of the science in the field of reproductive environmental health and its implications for OB/GYN clinical practice.

Recent findings

Women of childbearing age incur ubiquitous contact to numerous toxic environmental contaminants. Even subtle perturbations caused by chemical exposures during critical and sensitive windows of development may lead to increased risks of disease and disability across the entire span of human life. The strength of the evidence is sufficiently high that leading scientists and clinicians have called for timely action to prevent harm.

Summary

OB/GYNs are uniquely poised to intervene in critical stages of human development (i.e., preconception and during pregnancy) to prevent harm. Efforts are underway to provide clinicians with the evidence-based foundation to develop recommendations for prevention. If adopted, current directions in toxicity testing, risk assessment and policy are likely to create important changes in how environmental chemicals are evaluated and regulated in the future. Together, these changes have the potential to assist in clinical assessment of patient risk and reductions in patient exposure to environmental contaminants linked to adverse reproductive health outcomes.

Keywords

critical windows of development, developmental origins of disease and health, environmental contaminants, reproductive environmental health

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Introduction

The fact that exposure to chemicals can harm human reproduction has been known since Roman times when lead was first recognized to cause miscarriage and infertility in women and men [1,2]. Over the past 60 years it has become clear that the placenta does not protect the fetus from damaging chemicals, that the fetus can be uniquely sensitive to chemical exposures, and that inter-generational harm can result from in-utero chemical exposures.

Examples of human evidence that documents key principles in reproductive environmental health are as follows.

- (1) The placenta does not protect the fetus from damaging chemicals: methylmercury. In the 1950s, methylmercury exposure *in utero* resulted in severe neonatal neurological impairment in children after pregnant mothers consumed high levels of methylmercury in fish and shellfish contaminated from toxic

industrial releases in Minimata, Japan [3]. More recent evidence documents that developmental and cognitive effects can occur in children exposed prenatally to mercury at low doses that do not result in effects in the mother [4–7], and that the adverse neurological effects of methylmercury exposure may be delayed [8,9]. As of 1992 there were 2252 officially recognized cases of Minimata disease [10].

- (2) The fetus can be uniquely sensitive to chemical exposures: thalidomide. In the 1960s, thalidomide, a drug given to pregnant women for morning sickness, with no adverse maternal consequences, resulted in a high rate of congenital limb and gastrointestinal malformations when taken day 28–42 post conception [11,12]. It is estimated that more than 10 000 children in 46 countries where the drug had been approved were born with deformities as a consequence of their mothers using the drug during pregnancy [13].
- (3) Intergenerational harm can result from in-utero chemical exposures: diethylstilbestrol (DES). DES, which was prescribed in up to 10 million pregnancies

from 1938 to 1971 to prevent miscarriage, was subsequently found to be a 'transplacental carcinogen' causally linked to postpubertal benign and malignant reproductive tract abnormalities in the daughters and sons of DES-exposed mothers. These adverse health impacts manifested only decades after exposure [14]. Established health impacts of in-utero DES exposure include: vaginal clear cell adenocarcinoma, vaginal epithelial changes, reproductive tract abnormalities (e.g., gross anatomical changes of the cervix, T-shaped and hypoplastic uteri), ectopic pregnancies, miscarriages, and premature births, and infertility in females exposed *in utero*; reproductive tract abnormalities (e.g., epididymal cysts, hypoplastic testis, cryptorchidism) in males exposed *in utero*; and increased risk for breast cancer in women who took the drug while pregnant [15]. Recent cohort studies indicate that women who were exposed to DES prenatally have an increased risk of breast cancer after age 40 [16]. Animal data predict intergenerational impacts (i.e., among granddaughters of DES-exposed women) to-date supported by limited human data [17].

These discoveries stemmed from exposure to drugs and higher levels of environmental chemical exposure than typically encountered by the general population. Hence it was generally assumed that environmental exposures experienced by an average person living in the U.S. would be below levels of reproductive harm.

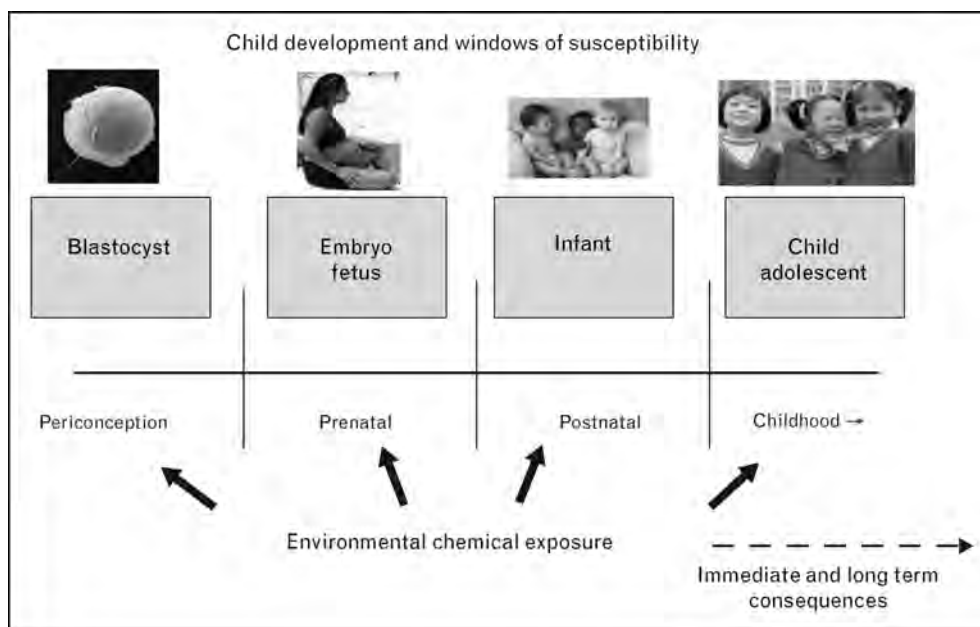
A rapidly expanding body of scientific evidence has upended assumptions about the benign nature of 'low-level' environmental exposures [18[•],19[•],20,21]. We now know that even subtle perturbations caused by chemical exposures may lead to important functional deficits and increased risks of disease and disability across the entire span of human life, particularly when exposure occurs during critical and sensitive windows of development (Fig. 1) [22–25,26^{••},27^{••}].

'Reproductive environmental health' addresses exposures to environmental contaminants (synthetic chemicals and metals), particularly during critical and sensitive periods of development and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health [27^{••}]. This article provides an overview of the nature and extent of the science in the field of reproductive environmental health and its implications for OB/GYN clinical practice.

Trends in reproductive health

Scientific indicators of declining reproductive function and increasing rates of reproductive illnesses since the mid-20th century suggest our reproductive health and, ultimately, our reproductive capacity are under strain [25,27^{••},28,29]. A spectrum of female and male reproductive disorders as well as poor birth outcomes and

Figure 1 Windows of susceptibility



Modified with permission from Louis *et al.* [22].

Table 1 Trends in reproductive health indicators

	Reproductive diseases/disorders	Increase	Period	Location	Reference
↑	Testicular cancer	1–6%	1953–1999	Europe	[35]
	Testicular cancer	60%	1973–2003	USA	[36]
	Certain childhood cancers	20–24%	1976–2005	USA	[37]
	Autism	57%	2002–2006	USA	[38]
	Attention deficit hyperactivity disorder	3% per year	1997–2006	USA	[39]
	Birth defects				
	Cryptorchidism	200%	1970–1993	USA	[40]
	Gastroschisis	300%	1978–2005	California	[41]
	Congenital hypothyroidism	138%	1987–2003	New York	[42]
	Reproductive function	Increase	Time	Location	References
↓	Reported difficulty conceiving and maintaining pregnancy				
	All ages	60% more women	1982–2002	USA	(K. Brett, personal communication)
	<25 years old	200% more women	1982–2002	USA	(K. Brett, personal communication)
	Prematurity	2.9% shorter gestation	1992–2002	USA	[44]
	Preeclampsia	19–36%	1968–2002	Norway	[45]
	Gestational diabetes	122%	1989–2004	USA	[46]
	Premature puberty				
	Age at onset of breast development	1–2 years younger	1940–1994	USA, Denmark	[47,48]
	Age at onset of menstruation	2.5–4 months younger	1940–1994	USA	[47]
	Sperm count	~1% decline per year	1931–1994	Western countries	[49,50]
	Serum testosterone	1% decline per year	1987–2004	Boston, USA	[51]

Modified with permission from [30*].

childhood disorders are increasing [30*,31*]. The burgeoning evidence from human populations is further amplified by signals from wildlife showing birth defects and other altered reproductive performance in wild populations of annelids, mollusks, crustaceans, insects, fish, amphibians, and other species [32,33*,34*,35–51] (Table 1) (K. Brett, personal communication).

These trends in reproductive health have occurred in roughly the same time frame in which human exposure to both natural and synthetic chemicals has dramatically increased. Approximately 87 000 chemical substances are registered for use in U.S. commerce as of 2006, with about 3000 chemicals manufactured or imported in excess of 1 million pounds each [52], and 700 new industrial chemicals introduced into commerce each year [53*].

Today, women of childbearing age have ubiquitous contact to toxic environmental contaminants and their exposure can reach the fetus through placental transfer and continue to expose the newborn through breastfeeding [54**]. Population-based studies conducted by the U.S. Centers for Disease Control and Prevention (CDC) demonstrate widespread exposure to many chemicals found in homes, communities, and workplaces that can disrupt the normal functioning of hormones and/or have neurological or other toxicities [55,56*]. A recent analysis of CDC population prevalence data found virtually all pregnant women in the U.S. have body burdens of *all* of the following reproductive/developmental toxicants: lead, mercury, toluene, perchlorate, bis-phenol A (BPA), and some phthalates, pesticides, perfluorochemicals (PFCs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs) [57*]. Similar

findings from studies in Europe [58], and populations in the Arctic far from pollution sources [59*], indicate that all human populations are exposed to some level of synthetic chemicals.

Developmental origins of health and disease

The body of evidence linking environmental exposure or other stimulus or insult during a critical period of growth and development to the propensity to develop disease or dysfunction later in life evolved independently in the fields of nutrition and environmental health [17*,60*]. In the field of nutrition, the hypothesis of ‘developmental programming’ stemmed from epidemiologic studies beginning in the mid-1980s in the UK by Barker and Osmond [61–64], who identified strong relationships between maternal under-nutrition, low birth weight and long-term risk of metabolic disease. A large body of experimental and epidemiologic data have substantiated and further refined scientific understanding of these linkages [17*,60*].

In 1971, the transplacental carcinogenicity of in-utero exposure to a synthetic nonsteroidal pharmaceutical with estrogenic activity was first identified, and DES remains one of the most scientifically robust illustrations of the linkage between developmental exposure to a hormonally active exogenous chemical and latent onset of adult disease [17*]. Since the latter part of the 20th century ‘endocrine disrupting chemicals’ (EDCs) beyond DES have received increased scrutiny because they are ubiquitous in the environment, hormonal regulation is critical to human reproduction and development, and chemicals that interfere with this process can cause permanent disruption [28,65].

The U.S. Environmental Protection Agency (USEPA) defines endocrine disruptors as compounds which ‘interfere with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis (normal cell metabolism), reproduction, development, and/or behavior’.

Examples of EDCs commonly found in food, water, air, house dust, and/or personal care products include phthalates, BPA, PBDEs, perchlorate, and some pesticides.

Between 2007 and 2010, four major scientific reviews/proceedings examined the state of the science regarding the relationship between exposure to environment contaminants and human reproductive health and all concluded that while many scientific questions remain, the current evidence warrants timely action to prevent harm [26^{••},27^{••},54^{••},66^{••}]. A key point of intersection of these four efforts is the critical mass of scientific evidence that the embryo, fetus, and developing human are highly vulnerable to exposure to even small amounts of environmental toxicants [26^{••},27^{••},54^{••},66^{••}].

For example, in 2009, the Endocrine Society, the premier professional organization devoted to research on hormones and the clinical practice of endocrinology, conducted a comprehensive review of the human and experimental evidence linking environmental exposure to EDCs to human health. The Endocrine Society review concluded, ‘The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis’ [54^{••}]. Subsequently, evidence that strengthens these conclusions has continued to mount, exemplified by the first animal evidence to report a link between neonatal exposure to high doses of BPA with development of polycystic ovarian syndrome-like abnormalities in adulthood [67[•]] and epidemiologic evidence confirming the role of prenatal exposure to pesticides and childhood neurobehavioral deficits [68[•]], and childhood leukemia (30–200% increased risk) [69[•],70[•]].

Epigenetics

While it has long been known that genetic mutations can alter gene expression and lead to disease (i.e., ionizing radiation), the field of ‘epigenetics’ has greatly extended our understanding of the mechanisms through which EDCs and other environmental contaminants can perturb the fetal environment and influence health throughout the lifecourse [71[•]]. ‘Epigenetics’ includes any process that alters gene activity without mutating the DNA sequence, and leads to modifications that can be transmitted to

daughter cells [72]. Environmental modifications of gene expression can affect embryonic imprinting, cellular differentiation, and phenotypic expression [73]. Nascent human research has begun to expand mechanistic data from animal studies on the effect of chemical contaminants on the epigenome and human health [74[•],75[•]].

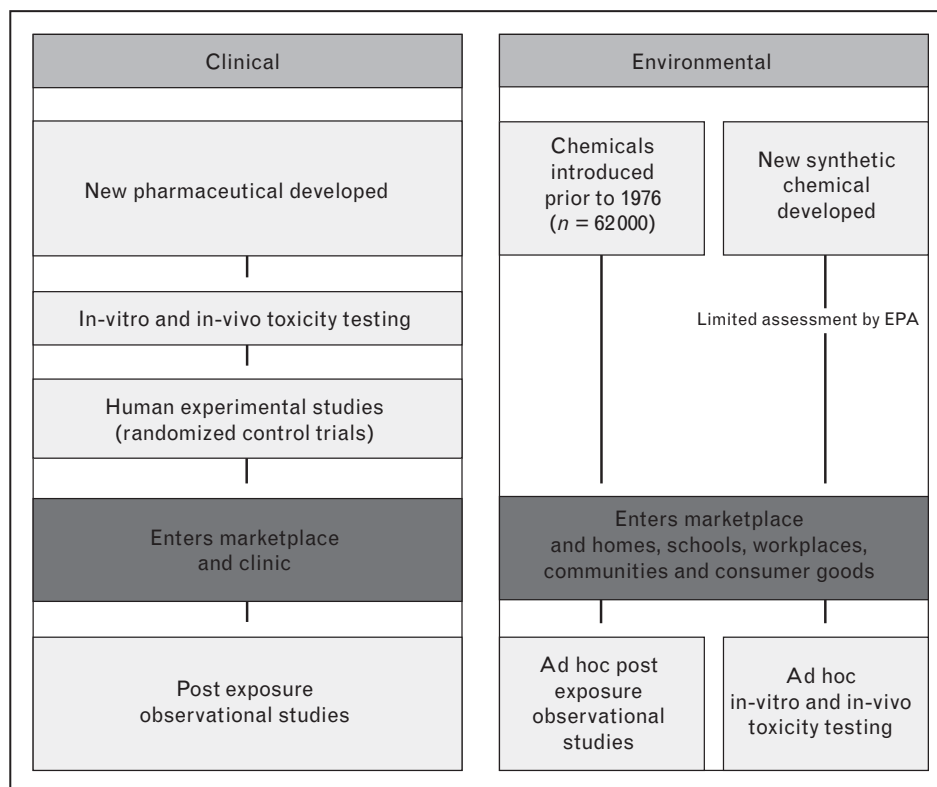
Implications for OB/GYN clinical practice

Current research in reproductive environmental health is inextricably linked to healthy pregnancies, children, and future generations but the science has yet to be harnessed to improvements in patient outcomes. Among physicians, OB/GYNs are uniquely poised to intervene in critical stages of human development (i.e., preconception and during pregnancy) to prevent harm. Healthcare professionals are increasingly called on to serve as a science-based source of guidance on how to avoid potentially adverse exposures [76,77[•]]. Many OB/GYN patients are already asking questions about their exposure to environmental contaminants and many more lack awareness of potential environmental risks to their fertility and their future children’s health. The role of clinicians extends beyond the clinic walls [78[•]]. In 2009, the Endocrine Society recommended that ‘Until such time as conclusive scientific evidence exists to either prove or disprove harmful effects of substances, a precautionary approach should be taken in the formulation of EDC (endocrine-disrupting chemicals) policy’ [54^{••}]. Subsequently, the American Medical Association (AMA) adopted a resolution that reflected the findings and recommendations of the Endocrine Society’s review and called on the AMA to work with the federal government to enact new policies to decrease the public exposure to EDCs.

Bridging the gap between environmental and clinical health sciences

One key challenge to translating the state of the evidence linking exposure to environmental toxicants to human health into clinical practice is that the evidence stream and decision context in environmental health sciences differs from clinical sciences and practice. In the clinical setting, in-vivo, in-vitro, and human experimental evidence and an analysis of risks and benefits have informed human exposure decisions prior to the substances’ entry into the marketplace (Fig. 2). In stark contrast, population exposure to exogenous substances in the environment typically occurs prior to regulatory scrutiny of a compound and in the absence of risk–benefit analysis because of our current regulatory structure for governing manufactured chemicals (Fig. 2). Ethical considerations virtually preclude experimental human data from the environmental health evidence stream.

To help bridge this gap between environmental and clinical health sciences, in 2009, the University of

Figure 2 Comparison of streams of evidence in clinical and environmental health sciences

California, San Francisco, Program on Reproductive Health and the Environment undertook a collaborative project to craft the *Navigation Guide*, a methodology to provide the evidence-based foundation for the development of recommendations for prevention [Sutton P, Coglian VJ, Guyton K, *et al.* The navigation guide: an evidence-based methodology to support clinical recommendations about the potential risks to reproductive health from exposure to chemicals in the environment, in preparation (the study describes the first methodology to link an evidence-based medicine framework to the evidence stream in environmental health sciences)]. The *Navigation Guide* is the product of a year-long collaboration of 22 clinical and environmental health scientists and/or practitioners, from governmental and nongovernmental organizations in the U.S. and Europe. The *Navigation Guide* proceeds from an evidence-based medicine framework but reflects the differences in evidence and decision contexts described above. Uptake of the *Navigation Guide* in clinical and policy arenas will provide a missing tool to support evidence-based decision making to ensure healthy pregnancies, children, and future generations.

Current directions in toxicity testing, risk assessment, and regulatory policy

Just as the thalidomide tragedy led to strengthened regulatory oversight of the safety and efficacy of all

prescription drugs [13], recent advances in toxicity testing [72,79], risk assessment [18[•],19[•],20,80], and policy [81] are likely to create important change in the way environmental chemicals are evaluated and regulated in the future.

Toxicity testing

Toxicity testing in the 21st century is anticipated to move away from identifying apical endpoints in animal models and towards identifying biologic perturbations in key toxicity pathways without the use of whole body animal testing [53[•]]. The proof of principle that it is feasible to move toward using upstream mechanistic indicators as the basis for risk assessment and decision-making was recently demonstrated for several classes of early perturbations, that is thyroid hormone disruption, antiandrogen effects, and immune system disruption [82]. This fundamental shift will align toxicity testing with clinical care which already recognizes the importance of perturbations in individual hormone levels to disease, for example, in the relationship between hypothyroidism during pregnancy and increase risk for neurocognitive deficits in children [83].

Assessing harm from chemical exposures

Assessing harm from exposure to environmental contaminants is rapidly moving beyond traditional methods that

generally look at how exposure to one chemical, acting through a dominant mechanism of action, can impact a healthy adult (T. Woodruff, in preparation). In 2008, the National Academy of Sciences (NAS) issued two groundbreaking reports concerning new science that extends our understanding of the relationship between exposure to environmental contaminants and health [18*,19*]. The NAS reports address the need to incorporate increased recognition of how concurrent chemical exposures, age, underlying health status, and other biological factors can modify risk [18*]; and move from a 'common mechanisms of action' approach to a 'common adverse outcome' focus, because there may be not just one but many pathways to the same adverse health outcome [19*]. The 'common adverse outcome' principle is exemplified by the health risk of exposure to phthalate esters, a class of ubiquitous chemicals used in a wide range of personal care and other consumer products. Phthalate esters disturb androgen action through multiple mechanisms which all lead to a common adverse health impact, that is altered male reproductive outcomes [19*]. Studies also show that exposure to other chemicals that act on the same common adverse health outcome, male reproductive development, but through different mechanisms, can have added effects [19*]. If adopted, these changes would accelerate our understanding of the health risks of current levels of exposure to environmental contaminants.

Policy

Just because a product is readily available on the shelf at the store is no assurance that it is nontoxic. The vast majority of chemicals in commerce have entered the marketplace without comprehensive and standardized information on their reproductive or other chronic toxicities (Fig. 2) [81]. The inadequacies of the regulatory framework are receiving increased attention. In 2007, 'REACH', a new European Community Regulation on chemicals and their safe use (EC 1907/2006) entered into force. In 2009, the USEPA established 'Essential Principles for Reform of Chemicals Management Legislation' to help inform legislative efforts now underway to reauthorize and significantly strengthen the effectiveness of chemical regulation [84*]. Because many exposures are not controllable at the individual level (e.g., air pollution), these society wide actions are critical to reducing exposure to harmful chemicals.

Conclusion

Women of childbearing age have ubiquitous exposure to toxic environmental contaminants. Exposure to environmental contaminants incurred during critical and sensitive windows of development can adversely impact the health of infants, children, women, men, and potentially future generations. While many scientific questions remain, the strength of the evidence is sufficiently high

that leading scientists and clinicians have called for timely action to prevent harm.

OB/GYNs are uniquely poised to intervene in critical stages of human development (i.e., preconception and during pregnancy) to prevent harm. Efforts are underway to provide clinicians with the evidence-based foundation to develop recommendations for prevention. If adopted, current directions in toxicity testing, risk assessment, and policy are likely to create important changes in how environmental chemicals are evaluated and regulated in the future. Together, these changes have the potential to assist in clinical assessment of patient risk and reductions in patient exposure to environmental contaminants linked to adverse reproductive health outcomes.

Acknowledgement

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 535–536).

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