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Toxic environmental chemicals: the role of reproductive health professionals in preventing harmful exposures

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Every pregnant woman in the United States is exposed to many and varied environmental chemicals. Rapidly accumulating scientific evidence documents that widespread exposure to environmental chemicals at levels that are encountered in daily life can impact reproductive and developmental health adversely. Preconception and prenatal exposure to environmental chemicals are of particular importance because they may have a profound and lasting impact on health across the life course. Thus, prevention of developmental exposures to environmental chemicals would benefit greatly from the active participation of reproductive health professionals in clinical and policy arenas.

Key words: environmental chemical, reproductive environmental health, toxic chemical

Among the US population, current indicators of reproductive adversity include a decline in the age of the onset of puberty,[1] declines in fertility and fecundity,[2,3] increased rates of poor birth outcomes (such as babies born prematurely[4,5]), increased rates of small for gestational age infants,[6] increased rates of certain birth defects,[7] and increased rates of childhood diseases (such as autism,[8] certain types of cancer,[9] and obesity[10]), and declines in life expectancy (some communities have life expectancies already well behind those of the best-performing nations[11]). Because these and other barometers of reproductive health and capacity have changed at a relatively rapid pace, they are unlikely to be explained by changes in genetic makeup.[12] Thus, we need to turn our attention to other factors that include the environment as possible contributors to these trends.

The environmental contributors to reproductive health begin in utero and include the social, physical, and nutritional environment and physical and chemical agents. Each of these factors interacts with the others and with intrinsic biologic factors (such as age, sex, and genes) to influence individual and population health outcomes.[13,14] For example, environmental pollution interacts with stress to the detriment of long-term health[15-17]; the effects of exposure to toxic chemicals can be exacerbated or mitigated by nutritional status,[18-20] and exposure to toxic chemicals and good nutrition is influenced by social and other environmental factors such as injustice, poverty, neighborhood, and housing.[18-25]

Disparities in these environmental contributors are of major health consequence.[26-28] Many communities with the highest exposures also lack access to medical care, good educational opportunities, good nutrition, employment, and other factors that may help to mitigate related impacts. Thus, the effect of a low-dose exposure to an environmental chemical may be quite different, depending on the population's degree of exposure to other environmental contaminants and underlying health status (Figure 1).[29]

Within the field of obstetrics and gynecology, preconception and prenatal exposure to environmental chemicals (which is defined in this article as including synthetic chemicals and metals) is a key area of inquiry because (1) exposure to many and varied toxic chemicals among pregnant women in the United States is now the norm (Figure 2),[30] (2) developmental exposure to certain environmental chemicals is linked to a myriad of health consequences that can manifest across the lifetime of individuals and potentially be transmitted to the next generation (Table),[57] and (3) exposure to environmental chemicals can be mitigated and prevented. This article provides a brief overview of this new science that is relevant to practicing obstetricians, gynecologists, and other reproductive health professionals and outlines opportunities for the prevention of harm and associated costs in clinical and policy venues.

Exposure to environmental chemicals among pregnant women

In the past 70 years, there has been a dramatic increase in human exposure to both natural and synthetic chemicals. Over this period, US chemical production and use has increased over 16-fold.[58] Today, >80,000 chemical substances are listed by the US Environmental Protection Agency (EPA) as manufactured or processed in the United States or imported into the country,[59,60] but this is probably an overestimate of the number of chemicals currently in commercial use. Approximately 3000-

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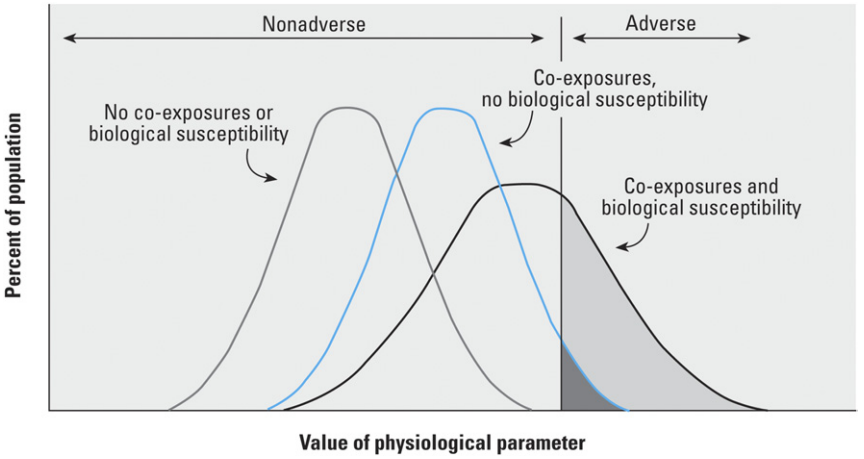
4000 chemicals are identified as high-volume chemicals, which means that >1 million pounds of each of them are manufactured or imported annually.[60] Moreover, approximately 700 new industrial chemicals are introduced each year.[61]

Health care professionals and the public cannot assume, as they do with pharmaceuticals, that adequate in vitro and in vivo testing of environmental chemicals has been undertaken and considered by regulatory agencies before widespread human exposure occurs (Figure 3). The vast majority of chemicals in commerce have entered the marketplace without comprehensive testing and standardized information on their reproductive or other chronic toxicities.[62,63] For example, in 1976 the US EPA was given the authority to regulate chemicals in commerce under the Toxic Substances and Control Act (TSCA). The EPA has used its authorities under the TSCA to require testing of <200 of the 62,000 chemicals in commerce when the TSCA became law.[64]

The inadequacy of our current regulatory framework for chemicals in commerce is recognized by physicians and organizations of health professionals (such as the American Medical Association and the American Academy of Pediatrics[65-67]), governmental[68] and nongovernmental organizations,[69] and industry.[70]

Toxic chemicals currently are distributed widely throughout homes, workplaces, and communities and contaminate food, water, air, and consumer products. A 2011 study that used population-based data from the National Health and Nutrition Examination Survey documented ubiquitous exposure among pregnant women in the United States to multiple chemicals.[30] The study found that virtually all pregnant women have measured levels of all of the following chemicals that can be harmful to human reproduction and/or development in their bodies: lead, mercury, toluene, perchlorate, bisphenol A (BPA), and some phthalates, pesticides, perfluorochemicals, polychlorinated biphenyls, and polybrominated diphenol ethers (PBDEs; Table).[30]

FIGURE 1
The effect of biologic susceptibility and coexposure to other chemicals on the relationship between individual chemical exposure and adverse health outcomes



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Several of these environmental chemicals in pregnant women, including phthalates, mercury, and PBDEs, are at levels that are associated with adverse health outcomes in human studies.[30] We have incomplete knowledge of what these exposures mean because the reproductive and other potential health impacts of daily exposure to this complex mixture of environmental chemicals have not been studied. This shortcoming is recognized by the National Academy of Sciences to be a gap in current scientific methods that inform public policy that permits human exposure.[29] The National Academy of Sciences has also concluded that, in the absence of data, one cannot assume (as policy makers and regulators currently do) that there is a threshold or safe limit of exposure for chemicals that adversely impact reproductive or developmental health outcomes.[29,79]

Many chemicals in pregnant women can cross the placenta; in some cases, such

FIGURE 2
Environmental chemicals in pregnant women in the United States

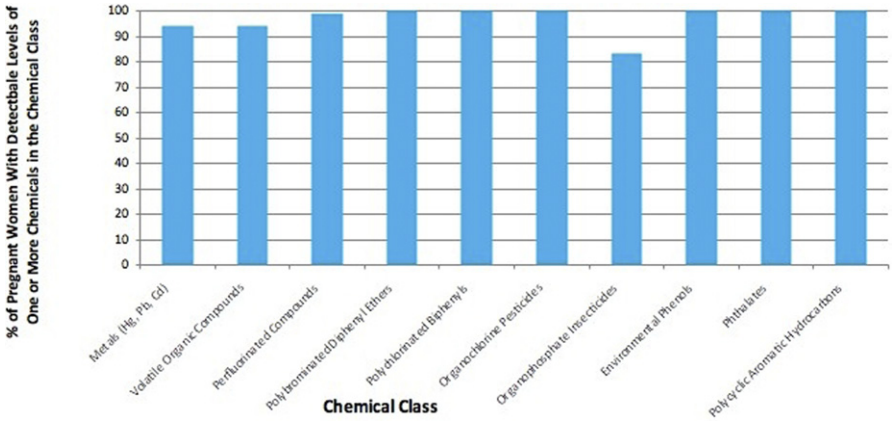

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TABLE
Examples of reproductive health impacts of prenatal exposure to environmental contaminants

Chemical	Exposure sources and pathways	Reproductive/developmental health impact
Bisphenol A	Chemical intermediate for polycarbonate plastic and resins; found in consumer products and packaging; exposure through inhalation, ingestion, and dermal absorption.	Recurrent miscarriage[31]
		Aggression and hyperactivity in female children[32]
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.	Alterations in genomic methylation[17]
		Increased likelihood of allergies[33]
Mercury	Coal-fired power plants are largest source in the United States; primary human exposure by consumption of contaminated seafood.	Reduced cognitive performance[34,35]
		Impaired neurodevelopment[36,37]
Polybrominated diphenylethers	Flame retardants that persist and bioaccumulate in the environment; found in furniture, textiles, carpeting, electronics and plastics that are mixed into, but not bound to, foam or plastic.	Impaired neurodevelopment[38]
		Premature delivery, low birthweight, and stillbirth[39]
Polychlorinated biphenyls	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.	Development of attention deficit–hyperactivity disorder–associated behavior[40]
		Increased body mass index[41]
		Reduced IQ[42]
Polyfluorochemicals	Widely used man-made organofluorine compounds with many diverse industrial and consumer product applications; examples are perfluorooctane sulfonate and perfluorooctanate, 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.	Reduced birthweight[43]
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[44]
Pesticides	Applied in large quantities in agricultural, community, and household settings; in 2001, >1.2 billion pounds of active ingredients were used in the United States; can be ingested, inhaled, and absorbed by the skin; pathways of exposure include food, water, air, dust, and soil.	Impaired cognitive development
		Impaired neurodevelopment[45,46]
		Impaired fetal growth[47]
		Increased susceptibility to testicular cancer[48]
		Childhood cancers[49]
Phthalates	Synthetically derived; used in a variety of consumer goods such medical devices, cleaning and building materials, personal care products, cosmetics, pharmaceuticals, food processing, and toys; exposure occurs through ingestion, inhalation, and dermal absorption.	Reduced masculine play in boys[50]
		Reduced anogenital distance[51]
		Shortened gestational age[52]
		Impaired neurodevelopment in girls[53]
Toluene	Exposure occurs from breathing contaminated workplace air, automobile exhaust, some consumer products such as paints, paint thinners, fingernail polish, lacquers, and adhesives.	Decreased fetal and birthweight[54]
		Congenital malformations[55,56]

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as methyl mercury, fetal exposure has been documented to be higher than maternal exposure.[72-74] In 2010, the National Cancer Institute's President's Report on Cancer observed that "to a disturbing extent babies are born 'pre-polluted'."[75] Postnatally, maternal exposure to environmental chemicals may continue to expose a newborn infant through breast-feeding.[76-78]

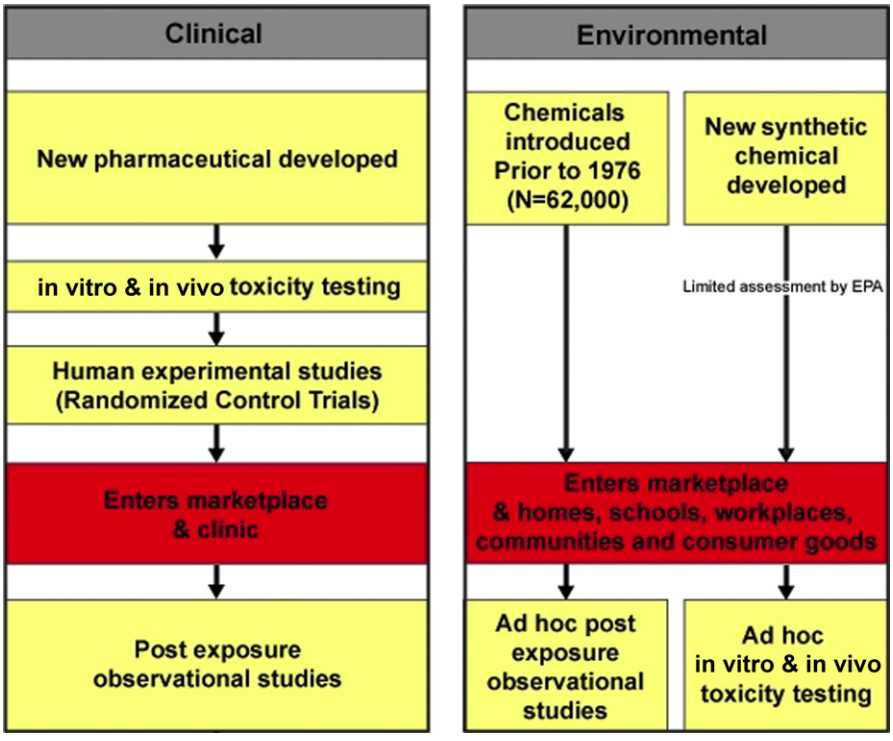
Developmental vulnerability to environmental chemicals

Assumptions about the benign nature of "low-level" environmental exposures have been upended by the new science.[29,79] We now know that the human reproductive system is particularly vulnerable to biologic perturbations that are caused by ambient levels of environmental chemicals when these exposures occur during critical or sensitive periods of development (ie, in utero and during infancy, childhood and adolescence).[80-82] This vulnerability is, in part, because these are times of extensive developmental changes, such as cellular proliferation and rapidly changing and/or undeveloped metabolic, hormonal, and immunologic capabilities.[83]

For example, critical stages of central nervous system development occur from embryogenesis through adolescence. The periods of neuronal proliferation, migration, differentiation, and synaptogenesis are especially sensitive to disruption and permanent damage.[84,85] Because these processes are unidirectional, interference at an early stage may result in disruption throughout the further cascade of reactions and interactions that propagate human development.[84,85]

The range of potential adverse impacts from in utero exposure to exogenous chemicals is already well understood by clinicians who are familiar with thalidomide's congenital limb and gastrointestinal malformations[86-88] and diethylstilbestrol's delayed effects of benign and malignant reproductive-tract abnormalities and increased risk of female breast cancer.[89-91] Diethylstilbestrol remains one of the most scientifically robust illustrations of the linkage between developmental exposure to a hormonally active exogenous chemical and adult disease.[83]

FIGURE 3
Comparison of the evidence streams that are needed in clinical and environmental health sciences for an exogenous chemical to enter the marketplace



EPA, Environmental Protection Agency.
Adapted, with permission, from Woodruff et al.[146]

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Of growing importance for patient health is that the exposure of pregnant women to endocrine-disrupting chemicals (EDCs) beyond diethylstilbestrol has proliferated, such that simultaneous exposure to many EDCs is ubiquitous among pregnant women in the United States today.[30] The EPA defines *EDCs* as compounds that 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.[92] Examples of EDCs that commonly are found in food, water, air, house dust, and/or personal care products include phthalates, BPA, PBDEs, perchlorate, and some pesticides.[93] Because hormonal regulation is critical to human reproduction, chemicals that perturb the system may cause permanent effects.[94-99]

For example, polychlorinated biphenyls and PBDEs can disrupt maternal thyroid function that is crucial for normal fetal development; in utero exposure to these chemicals has been associated with neurologic deficits in human and/or animal studies.[38,100,101] Phthalates can interfere with testosterone; studies in animals and humans indicate that exposure to certain phthalates during critical times of development can increase the risk of adverse male reproductive development (in rats, undescended testicles and cryptorchidism and, in humans, a relationship with subtle measures of feminization in boys of women who have higher phthalate exposures during pregnancy).[79]

The mechanisms of action that are related to developmental exposure to environmental toxicants are many and complex and can change depending on when in the pregnancy or other developmental stage the exposure or related insult oc-

curs.[102,103] For example, environmental chemicals can interfere with the development of normal fetal lung structure and function by perturbing a variety of transcription factors and morpho-regulatory molecules during critical developmental stages.[96]

Normal cell signaling can also be perturbed by EDCs, heavy metals, and other environmental chemicals through epigenetic mechanisms, which, although not changing DNA, disrupt gene expression that is integral to the orchestration of healthy human development.[13] The relationship between the human genome and the environment has been analogized as genes acting to "load the gun" or create the potential for adverse health outcomes and as the environment acting as the "trigger" that activates the physiologic or pathologic network of biologic reactions or events that are responsible for human health and disease.[13] Environmental modifications of gene expression can affect embryonic imprinting, cellular differentiation, and phenotypic expression.[104] Beckwith-Wiedemann, Prader-Willi, and Angelman are 3 syndromes that exemplify the significance of epigenetics in real life.[105-107]

Human research has begun to expand mechanistic data from animal studies on the effect of environmental chemicals on the epigenome and human health.[17,108] However, as with preclinical testing of pharmaceuticals, the nonhuman system of evidence is the preferred method for the documentation and development of prevention strategies that are related to the health impacts of developmental exposure to environmental chemicals, because these studies can be undertaken before human exposure.[109] Environmental contaminants are not intended for human use, and it is unethical knowingly to expose humans to these chemicals under experimental conditions to assess for harmful effects.

The Table presents examples of the reproductive and/or developmental health effects from human studies of in utero exposure to environmental chemicals that are common in pregnant women today. Exemplary of these data, in 2009, the Endocrine Society reviewed the evidence of health impacts from EDCs and concluded that "the evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to EDCs is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis."[76]

New scientific discoveries (ie, epigenetics, cell signaling, and developmental programming) document the vulnerability of the developing human to contemporary levels of environmental chemicals. Environmental exposures during fetal development may lead to changes in organ structure, function, and/or metabolism that are permanent and impact lifetime health risk. For the practicing clinician, the new science means that an important outcome of pregnancy is not only a healthy newborn infant but also a human being who is programmed optimally for health from infancy through old age.

Implications of the new science for reproductive health clinicians

The nature and extent of the relationship between reproductive health and environmental chemicals is unfolding rapidly. The current strength of the evidence that links ubiquitous exposure to environmental chemicals to adverse reproductive and developmental health outcomes is sufficiently robust that leading scientists and reproductive health and other clinical practitioners have called for timely action to prevent harm.[57,75,76,81] Among physicians, obstetricians and gynecologists are poised uniquely to intervene in critical stages of human development (ie, preconception and during pregnancy) to prevent harm.

Taking action to prevent harm in clinical settings

Obstetricians and gynecologists can serve as a science-based source of guidance on how to avoid potentially adverse exposures.[110,111] As in other areas of clinical practice, communication of the science and areas of uncertainties about environmental chemicals can provide patients with the information they need to make informed choices based on the evidence and their values and preferences. Studies that are related to the communication of the results of environmental chemicals in breast milk and other biomarkers lend empiric support to this approach.[112,113]

Pediatricians have long been attuned to the opportunity that clinical practice offers to identify, evaluate, and counsel patients about preventing harm from hazardous environmental exposures. The American Academy of Pediatrics has had an environmental health committee for more than one-half of a century and publishes a clinicians' handbook for the prevention of childhood diseases that are linked to environmental exposures.[114]

In light of the importance of preconception and prenatal environmental exposures to the health of the pregnancy and the child and adult that she or he will become, these pediatric approaches to the incorporation of environmental health into clinical care are equally applicable to reproductive health professionals. Based on our experience in clinical practice and through our engagement with health professionals, scientists, and the public, many patients who are pregnant or thinking about becoming pregnant are intensely and justifiably interested in their environmental exposures; at the same time, other women of childbearing age are unaware of the risk of their exposures. Clinicians should intervene as early as possible to prevent exposures during pregnancy by alerting patients to potential hazards and providing guidance on how to avoid toxic exposures. By the first prenatal care visit, disruptions of organogenesis may have already occurred.

Taking an exposure history is a key first step. Clinicians should always ask women of childbearing age about occupational exposures; the workplace may be an important source of toxic exposures among pregnant women. Legal exposure limits for most workplace chemicals are not designed to protect against harm to a pregnancy or the developing fetus. A variety of examples of how to take an exposure history exist[115-118] and can be found at http://prhe.ucsf.edu/prhe/clinical/index.html#eh.

Clinicians should provide anticipatory guidance to all patients with information about how to avoid toxic exposures at home, in the community, and at work. Information and resources about envi-

ronmental hazards can be incorporated successfully into childbirth class course curriculum to help women and men make optimal choices for themselves and their children.[119] Patient-centered brochures with tips for the prevention of toxic exposures and links to many additional resources can be found at http://prhe.ucsf.edu/prhe/toxicmatters.html.

Patient-centered actions can reduce body burdens of toxic chemicals. Research documents that, when children's diets change from conventional to organic food, the levels of pesticides in their bodies decline.[120] Likewise, recent studies found that avoiding canned food and other dietary sources of BPA can reduce measured levels of the chemical in children and adult family members[121] and that short-term changes in dietary behavior may decrease exposure to phthalates significantly.[122] It is important to recognize, however, that decisions on the individual level about avoiding toxic exposures are complex and often affected by external factors that limit making healthier choices.[123] Patient purchasing patterns can also send a signal to the marketplace that can help drive society-wide change. This was demonstrated by the burgeoning market in organic food,[124] in the explosion of the market for alternatives to BPA in food contact uses such as baby bottles,[125] and in the recent decision by Walmart Stores, Inc (Rogers, AR) to ban a flame retardant that is found in hundreds of consumer goods from its supply chain.[126]

In addition, although reproductive health professionals can be certain that the environment influences patient health, the idea of adding yet another topic to a clinician's "to-do" list is likely to seem daunting. The reality of severely constrained patient-contact time and the lack of a reimbursement mechanism is compounded by the fact that medical education for obstetricians and gynecologists thus far has been largely devoid of training in reproductive environmental health beyond the dangers of alcohol, tobacco, and recreational drugs. However, reproductive health professionals do not need to be experts in environmental health to provide useful information to patients and make referrals when hazardous exposures are identified. Existing clinical experience and expertise in the communication of the risks of treatment are also largely transferable to environmental health.

Many useful resources exist to support clinicians in communicating about environmental risks.[127] The Pediatric Environmental Health Specialty Units (PEHSUs) are a network of investigators across the United States who support clinical capacity that is related to environmental health.[128] The PEHSUs respond to requests for information throughout North America on the prevention, diagnosis, management, and treatment of environmentally related health effects in children and, as such, are poised to serve as a valuable resource for obstetricians and gynecologists in recognition of the inextricable relationship between reproductive and pediatric health.

Recent case examples in our (M.D.M.; T.J.W.; N.S.) experience include a woman who had a high blood lead level and was 16 weeks pregnant. She had an evaluation by public health workers with a home visit that did not identify a source and was referred to the PEHSU by her physician. We identified her use of an aruveydic medicine with a history of contamination with lead. We counseled her in general regarding possible health consequences for her baby and made her physician aware of the protocol for management of elevated blood lead in pregnancy. Another example was a mother and newborn infant who were identified as having elevated blood mercury levels. The PEHSU helped to determine that it was inorganic mercury and made the referral to the EPA region emergency response team who identified the source of mercury as face cream.

Taking action to prevent harm in policy settings

The role of clinicians in preventing exposure to environmental toxicants extends beyond the clinic or office setting.[129,130] Society-wide policy actions are essential for the reduction of toxic exposures to pregnant women and other vulnerable populations because many exposures are not controllable on an individual level (ie, from air and water). In addition, environmental justice issues that are related to exposures to toxic substances cannot be redressed sufficiently by individual action. For example, women and men who are exposed to pesticides at work and in agricultural communities incur substantively higher exposures than the US population overall.[131,132]

There are many examples that demonstrate that clinicians are in an excellent position to take action in policy settings. For example, our industrialized food system is associated with many and varied threats to reproductive and developmental health, including exposure to pesticides, chemical fertilizers, hormones in beef cattle, antimicrobials in beef cattle, swine, and poultry, fossil fuel consumption and climate change, toxic chemicals in food packaging and cookware, and the production and promotion of food that is unhealthy for pregnant women.[133] Policy interventions by the health care sector and physician' patient engagement offer mutually reinforcing opportunities to advance a healthy food system as a strategy to prevent adverse reproductive health impacts.[133]

To this end, physician leaders have been instrumental in spurring efforts by health care institutions to support the development of urban agriculture programs, farmer's markets and local food-sourcing outlets to increase accessibility to healthier foods; health care institutions have undertaken procurement policies to create a sustainable and healthy food service model. Nearly 350 hospitals have taken the Healthy Food in Healthcare Pledge in support of these efforts.[134] Because the food system purchasing power of the health care system is so large (approximately $12 billion annually), clinicians who become engaged in changing their hospital food system procurement patterns can help leverage food system change more broadly. Other examples of institutional policy arenas for clinical action include the reduction of toxic chemicals in health care purchasing coupled to bringing policy gaps that impede less toxic procurement patterns to the attention of decision-makers (http://www.saferchemicals.org/resources/business/kaiser-permanente.html). Clinicians have also been engaged in reducing the use of pesticides in institutional pest-control

polices (http://www.mdpestnet.org/projects/ipmHealthcare.html).

Clinicians can also work towards policy change in their professional organizations. For example, professional organizations of physicians that include obstetricians and gynecologists have been active in calling for regulatory and other efforts to address exposure to toxic chemicals and many other environmental threats to human health. A compilation can be found at http://www.prhe.ucsf.edu/prhe/pdfs/ProfessionalStatementsDatabase.pdf.

In 2009, the Endocrine Society issued a position paper calling for improved public policy to identify and regulate EDCs and finding that "[u]ntil 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 policy."[99] The application of the precautionary principle in environmental health dates to the 1980s, and today precaution is an underlying principle of environmental health policy in the European Union, particularly in the realm of risk management.[135] The precautionary principle is defined in the following manner: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."[136] Reversing the burden of proof so that chemical exposures are not presumed safe in the absence of scientific evidence would exemplify a precautionary approach to environmental chemicals.

Future directions

Just as the thalidomide tragedy led to strengthened regulatory oversight of the safety and efficacy of all prescription drugs,[86] recent advances in toxicity testing,[137-142] risk assessment,[29,71,79,143,144] and efforts to address shortcomings in regulatory policy that is related to chemicals in commerce[68-70,145] are likely to create important change in the amount, type, and availability of chemical toxicity data and related health impacts. These anticipated improvements underscore the need for a method to ensure the timely application of these data to prevention. To this end, a method has been developed to evaluate the quality of evidence and strength of recommendations about the relationship between the environment and reproductive health in uniform, simple, and transparent summaries that integrate the best practices of evaluation in environmental and clinical health sciences.[146] The generation of clinical guidelines must proceed with the development and dissemination of validated methods to screen and counsel patients about their exposures and safer alternatives that will prevent exposure for all patients.

It is also expected that electronic medical records will revolutionize medical research by facilitating instant, comprehensive data that go back years into history and extend longitudinally into the future.[147] Harnessing these changes could greatly accelerate the creation of knowledge about the impact of the environment on our reproductive health and capacity. Obstetricians, gynecologists, and other reproductive health professionals can play a groundbreaking role by intervening in critical stages of human development to translate the new science into healthier pregnancies, healthier children, and healthy future generations. ■

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