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Advancing the Science of Environmental Exposures During Pregnancy and the Gene–Environment through the National Children's Study

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Abstract

In this article we provide nurses with information on the importance of studying environmental exposures during fetal, infant, and childhood development in the National Children's Study. Nurses should be aware of this study to aid in mitigating the complex health problems that arise from environment–health interactions. Nurses may help to educate the public, patients, and caregivers and are in an ideal position to be strong advocates for policy change and regulatory monitoring and enforcement.

Keywords

environmental exposure; reproductive epidemiology; National Children's Study

Agrowing recognition that children may be more susceptible than adults to exposures to toxins has led to the development of the large scale National Children's Study (NCS) to further understand the effects of environmental exposure. The NCS uses a longitudinal cohort to evaluate the effects of environmental exposure on the health and development of 100,000 children enrolled from birth to age 21 (Landrigan, Trasande, & Thorpe, 2006). The main objective is to learn about environmental and genetic factors influencing the risk for conditions such as asthma, autism, diabetes, obesity, and attention and learning disabilities (NCS, 2012). Organizations involved in this study are The National Institute of Child Health and Human Development (NICHD), the Centers for Disease Control and Prevention (CDC), and the U.S. Environmental Protection Agency (EPA).

The need for a children's study of this magnitude was recognized in the 1990s with growing evidence that fetuses, infants, and children are particularly vulnerable to environmental

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exposure, with health effects appearing years later (Wascham, 2009). *Exposure* is defined as contact between an agent and a target; contact takes place at an exposure surface over an exposure period (World Health Organization, 2002; Zartarian, Ott, & Dunn, 1997). The ability of children to metabolize and excrete certain agents is different than adults and therefore may result in more biological disruptions. More specifically, we know children are being exposed to >80,000 synthetic chemicals, the majority developed since the 1950s (Landrigan et al., 2006). These chemicals include plastics, pesticides, antibiotics, flame retardants, and synthetic hormones (Landrigan et al.). The U.S. Department of Health and Human Services (USDHHS) has elevated environmental health to a national priority and urged health promotion for all through a healthy environment that includes outdoor air and water quality, healthy homes and communities, and global environmental health (National Institute of Environmental Health and Safety [NIEHS], 2006; USDHHS, 2000). The NCS will be the largest and most comprehensive study of children's health ever conducted in the United States, and the ultimate goal is to develop prevention strategies and appropriate public health guidelines to improve the health of families and children (NCS, 2012).

Researchers in the NCS will use a national probability sampling approach based on counties within the United States (Landrigan et al., 2006; Landrigan, Raugh, & Galvez, 2010). Environmental exposure histories and biological data will be obtained during pregnancy from each mother enrolled in the study. Newborns will be assessed at birth, and samples of cord blood and placenta will be collected. The children in the study will be regularly examined as they grow (Landrigan et al., 2010). The NCS will form the basis of child-health guidance and policy in the United States, as it addresses critical questions in the area of environmental health and the long-term health effects of environmental exposure early in life (Landrigan et al., 2010).

Researchers in the NCS will investigate the impact of environmental exposures during pregnancy on children's health. The purpose of this article is to provide nurses with information on the NCS and how this study may affect infant and childhood health.

Environmental Exposure

According to the EPA (2011), *environmental exposure* is defined as the exposure to potentially harmful chemical, physical, or biological agents in the environment or to environmental factors that may include ionizing radiation, pathogenic organisms, or toxic chemicals. Chronic exposure can be broken down into continuous, intermittent, or episodic. Continuous exposure is a similar exposure repeated over time. Intermittent exposure is a small or large exposure that occurs more than once over a period of time at defined intervals. Episodic exposure is typically large and occurs more than once over a long period of time but at unknown intervals (e.g., dust particles released during building demolitions) (EPA).

A broad model depicting the pathway from an environmental exposure to a biological response, manifested by measurable health outcomes, is illustrated in Figure 1. The response begins first with contact between a target (individual) and an agent (chemical, biological, physical, radiological), in one or more media (air, water, soil, dust, fluids), by one or more pathways (inhalation, dermal, ingestion), at one time (acute) or over a period of time

(chronic). Although the model may appear simple, large gaps of knowledge exist due to the multidimensional aspects of exposure to environmental agents. Such unknowns include the following: What dosages of the various agents create toxicity? What are the latency periods from exposure to the agent and type of media to exposure response or manifestation of disease? Through the NCS, the investigation of environmental exposure in the context of fetuses, infants, and children promises to advance science, including nursing science. Translation of research findings to evidence-based perinatal and pediatric nursing interventions will be important.

Environmental Reproductive Epidemiology: Exposures in Utero and Suspected Teratogens

The field of reproductive environmental epidemiology expanded tremendously since 1961 when thalidomide, a drug used to treat morning sickness, was shown to cause birth defects (Selevan, 1991). Seeking to elucidate the mechanism of action in thalidomide teratogenesis has led to the publication of 2,000 papers, yet the exact mechanism of action remains unknown (Stephens, Bundle, & Fillmore, 2000). Thus, environmental epidemiology has evolved into an important branch of epidemiology that investigates why and how environmental factors, such as biological agents (pathogens), physical and chemical (radiation, lead and mercury, volatile organic compounds, and pesticides) affect health (Merrill, 2010).

Research evidence demonstrates that environmental exposure beginning in utero can affect infant, childhood, and adult health conditions (Burton, Barker, Moffett, & Thornburg, 2011; Merrill, 2010). Infants defined as younger than age 2, neonates defined as younger than 4 weeks, and children ages 6 to 12 are particularly susceptible to the toxic effects of environmental exposure (Au, 2002). Despite this growing area of concern, incomplete scientific evidence about the long-term consequences of exposure to environmental agents exists. Therefore, the NCS will be useful to guide primary prevention activities that reduce the opportunity for exposure, which is the first and most important line of defense to protect children's health.

Chemical Exposures

The effects of environmental chemicals on reproductive health are largely unknown (Yang, Needham, & Barr, 2005). Several environmental chemicals are known to affect hormonal activity, and their effects have been demonstrated in animal studies (Goldman, Laws, Balchak, Cooper, & Kavlock, 2000; NIEHS, 2011; Stoker, Parks, Gray, & Cooper, 2000). The NCS will include the study of a wide variety of chemicals, including suspected eco-estrogens such as perfluorochemicals (PFCs), phytoestrogens, bisphenol A (BPA), and phthalates (Hellerstedt, McGovern, Fontaine, Oberg, & Cordes, 2008).

Perfluorinated chemicals (PFCs) are compounds used in products such as nonstick cookware and fabrics that are resistant to heat, oil, grease, and water (Lau et al., 2007). Evidence that PFCs are associated with adverse reproductive health is inconclusive (Apelberg et al., 2007; Inoue, Okada, & Ito, 2004). However, animal studies have demonstrated that the fetus and

neonate are sensitive to PFC exposures, and further research is needed to explore the impact on the developing fetus and children (EPA, 2012).

Phytoestrogens are naturally derived from plant sources commonly found in soy products. These chemicals have notable estrogenic activity and have been investigated for their association with altered time of onset of puberty (Yang et al., 2005). Combined nutritional status, genetic predisposition, and environmental chemicals are associated with altered age at puberty (Yang et al.). The early onset of puberty is clinically and socially important to the population, as the early onset of thelarche is associated with an early diagnosis of breast cancer in susceptible populations (Hamilton & Mack, 2003; Yang et al.).

Bisphenol A (BPA) is used to make polycarbonate plastic products clear and shatter-proof (Hellerstedt, McGovern, Fontaine, Oberg, & Cordes, 2008). Adverse reproductive effects associated with BPA exposure include abnormalities in the female reproductive tract, early puberty, and alterations in mammary gland and uterus (Honma et al., 2002; Howdeshell, Hotchkiss, Thayer, Vandenberg, & vom Saal, 1999; Markey, Luque, Munoz De Toro, Sonnenschein, & Soto, 2001).

Phthalates are a group of chemicals that provide the soft and flexible characteristics of plastics and are found in many common consumer products such as perfume, hairspray, lotion, pacifiers, and food packaging (Pak & McCauley, 2007). As a result of their widespread use in common consumer products, exposure to these chemicals are ubiquitous in human populations (CDC, 2005). Birth defects have been associated with exposure to phthalates, particularly in male offspring; these defects include testicular atrophy, decreased anogenital distance, defects of penile structure, and reduced sperm count (Environmental Working Group, 2006; Swan et al., 2005; Toppari et al., 1996).

Additional research is required to determine the long-term effects of chronic, low-dose exposures to the aforementioned chemicals. Researchers in the NCS will study the interactions of these exposures along with individual susceptibility factors that underlie disease (Landrigan et al., 2006).

Gene–Environment Interactions

Understanding the impact of environmental exposure on human genetics and subsequent fetal and childhood health is an important first step in developing innovative nursing care to promote health in women and families. As almost all diseases result from complex interactions between an individual's genetic make-up and environmental agents. Subtle differences in genetic factors may cause people to respond differently to the same environmental exposure (Khoury, Davis, Gwinn, Lindegren, & Yoon, 2005). Exposure to environmental factors can have far-reaching, even cellular, effects on the developing fetus.

One of the most essential aspects of our environment is the accessibility of and the demands for energy (Wallace, 2010a). The flow of energy, mediated by mitochondria in the cell, is exclusively maternally inherited in humans. Only the mother provides the genetic information for mitochondria and the production of energy for her fetus through her oocyte (Giles, Blanc, Cann, & Wallace, 1980). At the moment of conception, the mother and the

interuterine environment she creates will have critical impact on the developing fetus. The fetus emerges from the interplay between energy, structure (anatomy), and genetic information (Wallace, 2010a). Gene–environment interaction is the interface between genetic and environmental factors (Dempfle et al., 2008).

The study of gene–environment interaction is important for improving accuracy and precision in the assessment of genetic and environmental influences. The NCS will explore gene–environment interaction with protocols to acquire biological samples from family members across multiple generations. This investigation will provide scientists with unique opportunities for linkage of genetic data with environmental measures from across generations (Landrigan et al., 2006). Toxic exposures may have specific effects on the fetus, infant, and child by epigenetic mechanisms.

Epigenetics

Epigenetics is a term from the 1940s used to describe how genes might interact with their surroundings to produce observable characteristics of an individual (Waddington, 1942). *Epigenetics* now refers to heritable traits that may occur over multiple rounds of cell division and sometimes transgenerational that do not involve changes to the underlying deoxyribonucleic acid (DNA) sequence (Cassidy & Allanson, 2010). The prefix *epi* or on top of helps explain that the epigenetic activity does not change a gene but rather covers it up or reveals it. The patterns of gene expression are governed by the epigenome, which sits on top of the genome. Epigenetics is a new field of emerging science in which researchers explore gene expression caused by mechanisms other than changes in the underlying DNA sequence (Cassidy & Allanson).

Extensive layers of cellular regulation occur for a gene to be transcribed, resulting in a protein product (Wallace, 2010b). These regulation activities are viewed as turning on and off of genes and have become the study of epigenetics. Human DNA is nuclear (nDNA) and mitochondrial (mtDNA) (Wallace, 2010b). Environmental factors can alter the heritable transcription states of nDNA and mtDNA and give rise to epigenetic effects (Wallace, 2010b). These heritable transcription states may be passed on from one generation to the next. For example, a pregnant woman may be exposed to a toxin, which can affect her, her fetus, and future offspring (Wallace, 2010b).

Epigenetic Systems

Several kinds of epigenetic systems have been identified (Chandler, 2007; Russo, Martienssen, & Riggs, 1996). The NCS, by design, incorporates the possible epigenetic influences on maternal, fetal, infant, child, and family health. Chromatin remodeling, methylation, RNA transcripts, and prions are a few of the multiple epigenetic mechanisms that can alter phenotype and cause disease in humans as discussed below.

Chromatin Remodeling—One way that genes are regulated is through chromatin remodeling (Chandler, 2007; Russo et al., 1996). Chromatin comprises DNA strands that wrap around structures called histones (Bird, 1986; Eberharter & Becker, 2002). Histone proteins are small spheres that connect to form a backbone that the DNA wraps around

forming the structure of the chromosome. If the shape or size of the histones is altered, DNA may either be more available for transcription or fold upon or kink resulting in less available for transcription. Thus, chromatin remodeling alters gene expression. Additionally, histones can be acetylated (acetyl molecules bind to histones), and this process is thought to improve access to genes and increase gene expression (Bird; Chandler; Eberharter & Becker; Russo et al.).

Methylation—Another epigenetic mechanism is methylation or the addition of methyl groups to DNA. Methyl molecules bind to DNA and block access to genes. Methyl groups may permanently activate or deactivate genes (Bird, 1986; Eberharter & Becker, 2002). Some areas of the genome are methylated more deeply than others, and heavily methylated stretches of DNA tend to be less transcriptionally active (Eberharter & Becker). Methylation patterns can also persist from the germ line of one of the parents into the zygote. This process marks the chromosome as being inherited from the mother or father and has been termed “genetic imprinting” (Cassidy & Allanson, 2010). The combined effects of histone modification and DNA methylation on gene expression has been described as the epigenetic code (Bird; Holliday, 1994). The epigenetic code may play a role in short-term adaptations of species to their environments by allowing for reversible phenotype variability (Rando & Verstrepen, 2007). For example, maternal methyl dietary supplements in mice affect epigenetic variation in the color, weight, and propensity for cancer in their offspring (Cooney, Dave, & Wolff, 2002; Waterland & Jirtle, 2003).

RNA Transcripts—Transcription is the process of creating a complementary Ribonucleic acid (RNA) copy of a sequence of DNA (Cassidy & Allanson, 2010). RNA and DNA are nucleic acids that use base pairs of nucleotides as a complementary language that can be converted back and forth from DNA to RNA by the action of the enzymes (Cassidy & Allanson). During transcription, a DNA sequence is read by RNA polymerase, which produces a complementary, antiparallel RNA strand. Transcription involves the unzipping of DNA, adding RNA nucleotides that are paired with complementary DNA and then untwisting the RNA+DNA helix and freeing the newly synthesized RNA strand (Cassidy & Allanson). Some epigenetic changes are mediated by the production of different forms of RNA or by the creation of a double helix RNA. Ribonucleic acid can be spread through diffusion from one cell to another. A large amount of RNA and protein is contributed to the zygote by the mother during oogenesis and results in maternal effect phenotypes (Mattick, Amaral, Dinger, Mercer, & Mehler, 2009).

Prions—Prions are infectious forms of protein that are capable of converting other native state versions of the same protein into a conformational infectious state (Yool & Edmunds, 1998). These prions or infectious proteins do not function like native proteins. They can alter phenotypes. Prions are considered epigenetic because they can be inherited but do not change the underlying DNA (Yool & Edmunds). Prion diseases or transmissible spongiform encephalopathies are a group of rare progressive neurodegenerative disorders that affect both humans and animals. They are differentiated by long incubation periods, and characteristic spongiform changes are associated with neuronal loss and a failure to induce inflammatory

response. Human prion diseases are Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, and kuru (CDC, 2011).

Implications for Practice

The time lag between initial environmental exposures and potential disease make it difficult to develop the extensive body of evidence needed to regulate many environmental hazards (Ashford & Miller, 1998). Observable adverse effects can occur years after exposure. As a result, the NCS will be useful in elucidating the effects of these exposures. At the same time, the NCS highlights the emerging science surrounding chronic low-level environmental exposure and the need for a new way of thinking about environmental contaminants and health.

Precautionary Principle

The adoption of the Precautionary Principle, a concept that has been popular in the European Union, is warranted. The concept can be stated as follows: 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 (Kriebel & Tickner, 2001). For instance, given the complex nature of endocrine disrupting compounds, the uncertainty of the impact of low-dose chronic exposures to chemicals, and the availability of certain alternatives (e.g., BPA or phthalate-free products), a precautionary approach on the part of the public is needed, particularly for children who are more susceptible to the effects of exposure.

The promotion of precautionary actions and primary prevention methods is one of the key responsibilities of nurses. As researchers help to investigate the role of environmental exposure in childhood disease, findings from the NCS may help to inform practice (Landrigan et al., 2006). For instance, sources and exposure agents may be identified through a pediatric environmental history-taking process (National Environmental Education and Training Foundation, 2006) or a pediatric environmental health assessment conducted during a home visit (National Center for Healthy Housing, 2007). To understand the exposure of a fetus/ infant/child, nurses may question how the exposure occurs. They may also consider attributes of the concentration of the hazardous agent in the environment of the mother and child and individual exposure factors. Table 1 lists reputable websites for current information on potential agents to which women may be exposed to during pregnancy and lactation. Clinicians should use Organization of Teratology Information Specialists (OTIS) and LactMed on a regular basis to assess safety of particular agents (e.g., drugs, pesticides, cosmetics, cleaning agents). Knowledge exists on some agents, but much more knowledge is needed so health care providers can translate the information about exposures in the environment into practice aimed at promoting optimal maternal and infant health outcomes.

Nurses have the opportunity to facilitate the identification of particularly susceptible individuals and populations for exposure and the development of interventions to reduce these exposures. For instance, when research suggested that phthalates in intravenous (IV) tubing were leaching into the fluids delivered to infants in the neonatal intensive care (NICU), well-informed nurses implemented a phthalate-free policy in their units to reduce

exposure for susceptible infants (Pak, Briscoe, & McCauley, 2006; Pak, Nailon, & McCauley, 2007). Nurses play an important role informing pregnant women about how to reduce in utero exposure. For example, many pregnant women may not be aware of the dangers from endocrine-disrupting chemicals (Pak & McCauley, 2007) and commonly used pesticides (Raugh et al., 2011; Whyatt et al., 2007). Nurses should educate women on the availability of phthalate-free personal care products and BPA-free alternatives and safe methods to control insects to reduce these exposures.

In addition, it is important for nurses to be cognizant of racial and ethnic disparities regarding environmental exposure. Low-income, disadvantaged, inner-city, marginalized minorities are at high risk for adverse birth outcomes and also are more likely to be exposed to environmental contaminants (Landrigan et al., 2010).

Recruiting and retaining approximately 1,000 to 1,250 families per study center will be important, and nurses are positioned to help the research team build relationships with families and encourage participation (Hellerstedt et al., 2008). Therefore, it is important that nurses are aware of NCS. Perinatal nurses are poised to provide strong leadership in environmental health for women and their families. Nursing professionals may help to educate the public, patients, and caregivers and are in an ideal position to advocate for policy change and regulatory monitoring and enforcement. Through the collaboration of nurses, physicians, and families, the NCS will help to improve the health and welfare of future generations.

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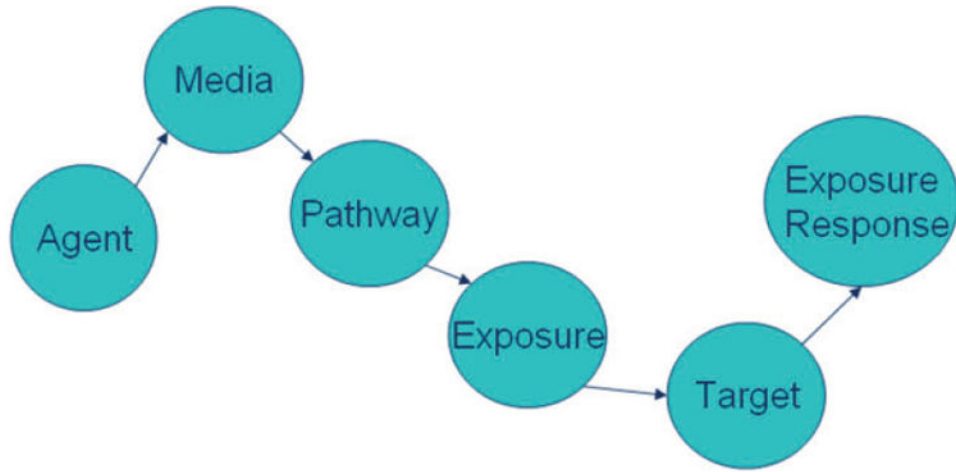


Figure 1.
Pathway from environmental agent exposure to environmental health response.

Table 1
Reputable Source of Information for the Most Current Information of Potential Exposures during Pregnancy and Lactation

Source	Function
Organization of Teratology Information Specialists (OTIS) http://www.otispregnancy.org/	OTIS provides accurate, evidence-based, clinical information to patients and health care professionals about exposures during pregnancy and lactation.
U.S. National Library of Medicine (LactMed) http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT	LactMed is a peer-reviewed database of drugs that provides information to health care providers and breastfeeding women or those considering breastfeeding regarding: drug levels, possible effects to the neonate, and possible drug alternatives.

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