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Wolters Kluwer

Overview of occupational and environmental risks to reproduction in females

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INTRODUCTION

Reproduction is a general term that applies to all aspects of procreation [1-5]. A reproductive hazard interferes with the ability of a couple to achieve a successful birth. Reproductive hazards affect fertility, conception, pregnancy, and/or delivery [6]. Development refers to the growth and maturation of the embryo, fetus, infant, and child. A congenital defect in an organ system or limb, or an intellectual deficit that becomes manifest after birth, are examples of adverse developmental effects. Occupational and environmental risks to the reproductive system are a concern to many patients and a high public health priority [1-3]. Well-known examples of devastating outcomes from exposure to teratogens include children born with limb malformations related to maternal use of [thalidomide](#) for insomnia or morning sickness, and children with severe neurologic problems related to maternal consumption of methyl mercury contaminated fish from Minamata Bay (Japan).

This topic will review types of reproductive hazards, types of adverse outcomes, and the mechanisms by which environmental factors can impact female reproduction. Related information on occupational and environmental health as well as the impact of specific agents on reproduction is presented in detail separately. (See "[Overview of occupational and environmental health](#)".)

BACKGROUND

Concerns have been fueled by reports and studies of problems regarding common environmental agents, including contaminants from plastics (such as bisphenol A and phthalates), chemicals that act as endocrine disruptors, polychlorinated biphenyls (PCBs), low-level lead and mercury exposures, perchlorate, pesticides, poly- and perfluoroalkyl substances, and air pollution [7,8]. Occupational exposures to these agents and others are also concerning since a large number of women in the United States and the world are engaged in occupations that have potential exposure to known or suspected reproductive toxicants [4,9,10]. Additional concerns have been raised about the toxic (and cumulative) effects of (low-level) exposures to the myriad industrial chemicals that are not regulated with the aim of protecting children [11,12].

Exposure to small amounts of potentially toxic chemicals is common. In a study of lead, mercury, and PCB blood levels among women of childbearing age (16 to 49 years) who participated in the National Health and Nutrition Examination Survey (NHANES), 33 percent had levels at or above the median for two of these chemicals and another 23 percent had blood levels at or above the median for three of these chemicals [13]. Although the levels of each individual agent were well below levels usually considered of clinical significance, the authors pointed out the need to study the effects of combinations of low level chemicals.

TYPES OF REPRODUCTIVE HAZARDS

The three general categories of reproductive hazards are (1) physical factors (eg, radiation, exposure to electrical shock, excessive vibration or heat, working conditions, and physical demands), (2) biological factors (eg, viruses, parasites), and (3) toxic agents (eg, toxicant exposure via ingestion, inhalation, or contact with skin). Some fetal toxicant exposures are concurrent with the pregnancy; however, others are the result of a previous (nonconcurrent) exposure, with ongoing maternal elimination of the toxicant or from mobilization of stored toxicants (eg, polychlorinated biphenyls from fat stores, lead from bone stores) [6].

TYPES OF ADVERSE OUTCOMES

Adverse reproductive and developmental outcomes from exposure to toxic agents include:

- Menstrual disorders and other hormonal influences
- Infertility
- Spontaneous abortion
- Stillbirth or infant death

- Low birth weight and fetal growth restriction
- Preterm birth
- Hypertensive disorders of pregnancy
- Congenital malformations
- Cognitive changes and reduced IQ
- Developmental delays
- Childhood cancer

Accurate data on baseline rates of specific adverse outcomes in the general population are difficult to assemble because of the absence of a national monitoring system in the United States and lack of comparability among epidemiologic studies. Estimated frequencies of various adverse outcomes in the United States are listed in the table ([table 1](#)) [4].

ASSESSING RISK

Specific environmental exposures have been linked to increased risks of the adverse outcomes discussed above. Yet the strength of the causal associations among exposures and outcomes also varies with the strength of the available data ([table 2](#)). Studies in humans that assess the causal relationship between specific exposures and reproductive outcomes frequently face limitations and challenges, including:

- Difficulty in accurately assessing the dose and timing of the exposure to mother and/or fetus
- Difficulties in accurate ascertainment of multiple co-exposures [4,14-17]
- Frequent lack of proper control groups since a variety of other genetic, physical, and socioeconomic factors affect reproductive toxicity
- Inadequate assessment of the background prevalence of events
- Difficulties with reliable ascertainment of the outcome or endpoint (eg, early abortion versus late heavy menses)

The effect of ascertainment bias was illustrated by a large cohort study that assessed occupational exposures mid-pregnancy by self-report of chemical agents and by use of a job-exposure matrix that linked job titles to workplace chemical exposures according to expert judgment [16]. After adjustment of confounders, the authors noted that self-reported exposures were not associated with an increased risk of adverse outcomes, but expert judgment-based exposure to phthalates was associated with prolonged time to pregnancy

(odds ratio [OR] 2.16, 95% CI 1.02-4.57) and pesticides were associated with decreased birth weight (OR 2.42, 95% CI 1.10-5.34), although the population attributable fractions were quite small (0.7 percent).

Potential problems also arise from study design. Ideally, a prenatal developmental toxicity study and a one-, two-, or multi-generation reproduction toxicity study are recommended for evaluating the reproductive hazard of a substance [18]. These types of studies are both cost- and time-intensive; thus, they are infrequently performed. A cross-sectional study that examines the relationship between adverse reproductive outcomes and exposures among current employees at a workplace may suffer from selection bias ("healthy worker effect") due to the lack of a representative population, since individuals with health problems may not be working, thus leaving only healthy individuals remaining at work. Alternatively, if workers able to conceive were out on pregnancy leave or performing child care, then the population remaining at work may be biased toward those with fertility problems.

A case-control design would be a good method for studying rare outcomes, such as congenital defects. Case control studies, however, are sometimes limited by the focus on one specific outcome (as reflected in the case definition), and thus miss identifying other potential adverse reproductive outcomes. They may also lack optimal exposure information. A prospective cohort design allows for better measurement of exposures and confounders from the outset, but may subsequently be limited if there is excessive drop out of study participants over time. Given the limited number of human studies, efforts have been made to look at pooled data, either using a strength of the evidence approach, or a more formal meta-analysis, in order to determine or rate the strength of the evidence in support of (or against) associations between specific exposures and adverse pregnancy outcomes [8,17,19].

Given limitations to high quality human data about adverse reproductive outcomes from specific agents and the large number of as yet untested chemicals, clinicians and governmental and regulatory agencies often turn to animal studies for information about potential toxicants. In evaluating the relevance of animal literature to humans, it is necessary "to consider the species tested; route, timing, and dose of exposure; end points examined; systemic or maternal toxicity; litter effects; consistency among animal studies; concordance with reproductive biology; and biological plausibility of a mechanism of action" [4].

With these caveats in mind, information concerning relationships of environmental exposures to adverse reproductive and developmental outcomes is discussed below. A general overview of occupational and environmental health, including how to take an environmental exposure history, is available separately. (See "[Overview of occupational and environmental health](#)".)

PATHOGENESIS

There are multiple physiologic events of reproduction that could be affected by environmental exposures [\[4,20\]](#).

Interference with oogenesis — It is thought that all primary oocytes of the human ovaries are formed by the fifth month of gestation, although one study of adult mice reported that new oocyte-containing follicles, presumably from stem cells, continue to develop [\[21\]](#). The oocytes begin their first meiotic division in utero, and then remain arrested until puberty when ovulation commences. Damage to oocytes during fetal development from toxicants, chemotherapy, or radiation may be manifested later in life as reduced fertility [\[4,6,22\]](#). Toxic exposures during the woman's lifetime also may induce genetic or cytotoxic harm to oocytes, even though they are equipped with an excellent (although not foolproof) repair system. (See ["Ovarian development and failure \(menopause\) in normal women"](#).)

Interference with the menstrual cycle and fertility — The menstrual cycle involves exquisitely timed rises and falls of follicle-stimulating hormone, luteinizing hormone, estrogen, and progesterone ([figure 1](#)) [\[4,10,22\]](#). (See ["Physiology of the normal menstrual cycle"](#).)

Toxicants may interfere with hormonal synthesis and secretion and thus lead to menstrual disorders, particularly disturbances in ovulation. In addition, some chemicals can mimic or disrupt the action of naturally occurring hormones and, as a consequence, lead to reproductive or developmental effects (see ["Occupational and environmental risks to reproduction in females: Specific exposures and impact", section on 'Bisphenol A and other phenols'](#)). Menstrual disorders have been reported among women in various occupations, including athletes, agricultural workers, lead exposed women, hairdressers, shift workers, and nurses handling antineoplastic drugs [\[23\]](#). Reduced fertility has been reported in dental assistants exposed to high levels of nitrous oxides [\[24\]](#), cleaners exposed to elevated levels of organic solvents, such as dry cleaning chemicals [\[25-27\]](#), and industrial workers exposed to drugs or chemicals during manufacture [\[23\]](#).

These relationships were illustrated in a study of ovarian function in Southeast Asian immigrant women in which daily urine samples were tested for organochlorine compounds (including DDT, its metabolite DDE, and 10 polychlorinated biphenyl (PCB) congeners) and hormone levels; menstrual cycle parameters were also assessed [\[28\]](#). DDE had effects on ovarian function (changes in cycle length, luteal phase length, level of progesterone metabolites) that could influence other endpoints such as fertility, pregnancy, and reproductive cancers.

Interference with fetal development — The dividing zygote reaches the uterus approximately three days after fertilization; implantation begins approximately three days later and takes approximately one week to complete. Toxic exposures during these first two weeks postconception usually result in fetal loss, which may appear as late menstrual flow. During this two-week period, the embryo is less sensitive to structural damage because sublethal damage can be corrected by cellular repair processes of the rapidly dividing cells.

From the third through the eighth week of development (the period of organogenesis), the embryo is very sensitive to teratogenic insults that cause abnormalities in form or function of a developing fetus. Environmental teratogens can produce cell death, alter normal growth of tissues, or interfere with normal cellular differentiation or other morphologic processes. The consequences of these actions can be fetal loss, fetal growth restriction, birth defects, or impaired neurologic performance.

Dose and timing are important determinants of fetal effects [29]. Thus, exposures occurring at "critical periods" in development have specific effects related to the developmental stage of the fetal organs ([figure 2](#)) and exposure to the same agent at different times may cause different anomalies. Exposures after the first trimester may induce only minor structural abnormalities, but can still impair growth (through effects on cell division and hypertrophy) and development (through effects on cell differentiation) occurring during the second and third trimesters. (See ["Birth defects: Approach to evaluation"](#).)

The fetal central nervous system (CNS) is the organ system most vulnerable to developmental injury throughout pregnancy [11-13,30]. The fetal brain is particularly sensitive to toxins because of the incomplete blood-brain barrier; continued myelination, proliferation and pruning of neurons; and sensitivity to hypoxia. Exposure to a neurotoxin can adversely affect both structural and cognitive development. Some toxins, such as mercury, lead, and tobacco, can exert these effects throughout gestation [31]. Prenatal exposure to numerous (low-level) environmental toxicants have been implicated as contributors to the development of neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, and other cognitive/behavioral impairments [12].

The relationship of genetic susceptibility, epigenetic changes, environmental exposures, and reproductive outcomes is an active area of investigation. As an example, a study in China observed that organic solvent exposure was significantly related to shortened gestation and that certain combined maternal-infant gene polymorphisms modified the effect of exposure to organic solvents on gestational age [32]. Gene-environment interactions, particularly DNA methylation and histone modifications ("epigenetic mechanisms"), also appear to have a role in

the development of neurologic and behavior function [33] and on development of asthma and allergic disease [34].

Effect of pregnancy — The physiologic changes of pregnancy may alter the amount of toxin absorbed and delivered to the fetus. As examples:

- Delayed gastric emptying and reduced intestinal motility increase absorption of ingested agents
- Increased minute ventilation and tidal volume increase absorption of respiratory toxins
- Increased plasma volume and total body water decrease the blood concentration of toxins
- Increased body fat decreases blood concentration, but increases fat storage, of lipid soluble agents
- Increased renal blood flow leads to increased renal excretion

Effect of maternal factors — The pregnant mother's overall health is also an important factor. If an exposure leads to direct toxicity to the mother, there may be indirect (as well as direct) adverse effects on the fetus. A mother with carbon monoxide poisoning or a severe asthma attack, as an example, may not adequately perfuse the placenta or release oxygen to the fetus. Some substances, such as mercury, may cause little or no clinical symptoms in the mother, but cause profound effects on the fetus (cerebral palsy, limb deformities, mental retardation, blindness and seizures) [35,36]. In addition, job-related physical or emotional stresses could impact the course of the pregnancy [4,35]. (See "[Working during pregnancy](#)".)

Effect of lactation — The American Academy of Pediatrics (AAP), the United States Preventive Medicine Task Force and the Centers for Disease Control and Prevention promote breastfeeding as the optimal form of nutrition for infants because of its advantages for general health and growth, and for its role in reducing risks of various acute and chronic illnesses [37,38]. Unfortunately, breast milk can sometimes be a source of contaminants [39-41]. This occurs when lactation mobilizes previously stored fat-soluble toxicants, such as dioxins, PCBs, some pesticides, and lead, which then diffuse into the mother's breast milk [42].

Maternal toxicokinetics, the solubility and binding properties of the toxicant, and the characteristics of breast milk determine the milk-maternal plasma (M/P) ratio [43]. The higher the ratio, the more substance is transferred into the breast milk. The M/P ratios for lipophilic substances like PCBs range from 4 to 10, whereas the ratio for organic and inorganic mercury is 0.9 [40]. Since infants rarely develop problems due to contaminants in breast milk, it is generally believed that the many benefits provided by breastfeeding outweigh risks from possible

contaminants [44]. The best approach is to strive for elimination of exposure to persistent bio-accumulating toxic chemicals in our environment. A study that measured volatile organic compounds (VOCs) in samples from a milk bank, in milk from three mothers in nonsmoking households, and from air in their homes found that their infants' average daily dose of VOCs was 25- to 135-fold higher by inhalation than by ingestion [45].

Of note, formula feeding does not guarantee an absence of contaminants, since water used in the formula can also contain contaminants, a particularly important consideration in developing countries.

IMPACT OF SPECIFIC ENVIRONMENTAL EXPOSURES

The impact of various exposures on reproduction are presented in detail separately. (See ["Occupational and environmental risks to reproduction in females: Specific exposures and impact".](#))

PREVENTION

Actions that patients can take to minimize their risk of exposure to occupational and environmental reproductive hazards include:

- Ask patients to identify potential hazardous exposures at work or at home, what protective measures (if any) are being used, and consider using available screening questionnaires or guides [46].
- Request copies and read the Material Safety Data Sheets (MSDS) for products to which they may be exposed. However, MSDS frequently have inadequate information about reproductive or developmental toxicity. Furthermore, the information may be inaccurate due to inherent limitations in acquiring these types of data [15].
- Use a safer product, if possible, to replace one that may be harmful in women planning pregnancy.
- Reduce or eliminate exposure through engineering controls or use of personal protection, such as protective clothing and respirators. Respirator usage later in pregnancy, however, may become difficult.
- When exposures cannot be controlled or eliminated, transfer the woman to a different job without the exposure.

- Avoid exposure to excessive vibration, temperature extremes, and ionizing and non-ionizing radiation.
- If chemical contact with the skin occurs, wash the area thoroughly as soon as possible.
- In general, work in well-ventilated areas and with proper control of chemical vapors or other toxicants.

RESOURCES

The number of agents with potential reproductive risks is too large to allow discussion of each within a monograph. The clinician can consult any of several resources that provide this information in a database. As an example:

- Pregnancy Exposure Hotline: 1-800-322-5014. This group is affiliated with The National Birth Defects Center in Waltham, MA and provides information, at no cost, on potential pregnancy risks from exposure to medications, chemicals, infections, radiation, and other agents.
- The University of California's (San Francisco) Program on Reproductive Health and the Environment focuses on the intersection of science, medicine, policy, and community engagement in each of our areas of activity: targeted research, expanding clinical practice, and advancing science-based policy solutions. Their website contains useful information at <http://prhe.ucsf.edu/>.
- National Library of Medicine (NLM) specialized information services on Developmental and Reproductive Toxicology. Available on-line at toxnet.nlm.nih.gov.
- REPROTOX is an information system developed by the Reproductive Toxicology Center. It contains commentaries on the potentially harmful effects of chemicals and physical agents on human pregnancy, reproduction, and development. It is available for a fee on-line (www.reprotox.org).
- Pediatric Environmental Health Specialty Unit (PEHSU), located in each of the 10 United States Environmental Protection Agency (EPA) regions. These provide education and consultation for health professionals, public health professionals and others about the topic of children's environmental health, including reproductive and developmental toxicity. Contact information for the sites can be found at www.pehsu.net.

SUMMARY AND RECOMMENDATIONS

- Adverse reproductive and developmental outcomes from exposure to toxic agents include menstrual disorders, infertility, spontaneous abortion, stillbirth or infant death, low birth weight and fetal growth restriction, preterm birth, congenital malformations, developmental delays, and childhood cancer. (See ['Types of adverse outcomes'](#) above.)
- While specific environmental exposures have been linked to increased risks of the adverse outcomes, the strength of the causal associations among exposures and outcomes also varies with the strength of the available data ([table 2](#)). Human studies frequently face limitations and challenges, including lack of accurate assessment of the dose of the exposure to mother and/or fetus; a need for proper control groups; inadequate assessment of the background prevalence of events; difficulties with reliable ascertainment of the outcome or endpoint (eg, early abortion versus late heavy menses); and difficulties in accurate ascertainment of exposures and multiplicity of exposures. (See ['Assessing risk'](#) above.)
- Multiple physiologic events that could be affected by environmental exposures include oogenesis, menstrual cyclicity, pregnancy, fetal development, and lactation. (See ['Pathogenesis'](#) above.)
- Individuals should take action to minimize their risk of exposure to occupational and environmental reproductive hazards. Such actions include (see ['Prevention'](#) above):
 - Identify potential hazardous exposures and reduce or eliminate exposure to these agents.
 - Request copies and read the Material Safety Data Sheets (MSDS) for relevant products.
 - Use the safest products available.
 - Avoid exposure to lead, mercury, excessive vibration, temperature extremes, and ionizing and nonionizing radiation.
 - Consider measures to avoid exposures to plastic contaminants.
 - If chemical contact with the skin occurs, wash the area thoroughly as soon as possible.
 - Work in well-ventilated areas and with proper control of chemical vapors or other toxicants.

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Topic 5447 Version 41.0

GRAPHICS

Prevalence of selected adverse reproductive outcomes in the United States

Outcome	Percent	Unit of measure
Infertility	8-12	Couples
Recognized spontaneous abortion	15-20	Women or pregnancies
Birth weight <2500 g	7-9	Livebirths
Preterm (≤ 37 wks)	11-13	Livebirths
Fetal death or stillbirth	0.7-1	Stillbirths and livebirths
Infant death	0.7	Livebirths
Birth defects (through 1 year of life)	3	Livebirths
Chromosomal anomalies in livebirths	0.2	Livebirths

Modified from: Janssen S. Female reproductive toxicology. Current Occupational & Environmental Medicine, 5th ed., Ladou J, Jarrison RJ (Eds), Lange Medical Books/ McGraw-Hill, New York 2014 and compiled from various sources.

Graphic 77872 Version 3.0

Agents with potential adverse effects on fetal growth

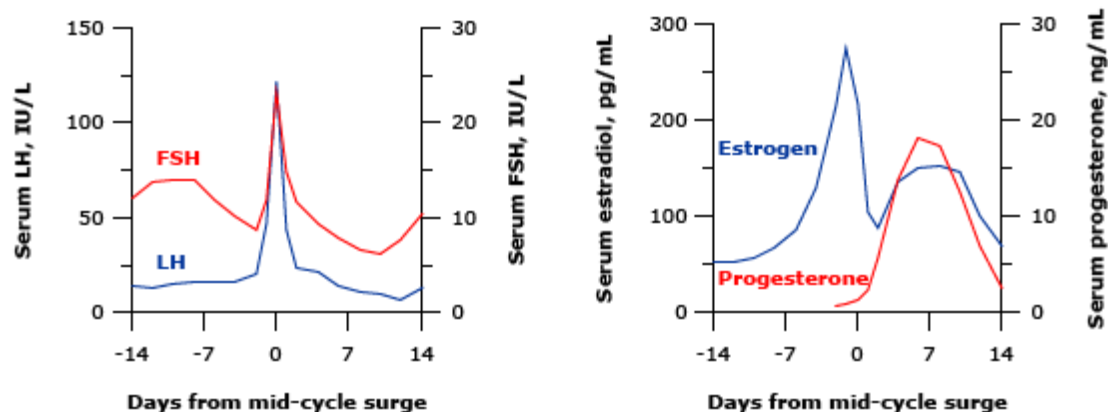
Selected agents with potential adverse effects on fetal growth or gestational age, by strength of evidence		
Limited	Moderate	Strong
Carbon tetrachloride	Air pollution	Carbon monoxide
Dioxins/TCDD	Herbicides	Cocaine
PCE/TCE (in water)	Metals (Pb, Hg, As)	Ethanol
Perfluorinated acids	Nicotine	Tobacco smoke
Phenoxyacetic	OC pesticides	
Herbicides	OP pesticides	
Phthalates	Pentachlorophenol	
	Biphenyls (PCBs)	
	Solvents	
	Water disinfection	
	Byproducts	

TCDD: 2,3,7,8- tetrachlorodibenzo para dioxin; PCE: perchloroethylene; TCE: trichloroethylene; Pb: lead; Hg: mercury; As: arsenic; OC: organo-chlorinated; OP: organophosphate; PCB: polychlorinated biphenyl.

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Graphic 99927 Version 2.0

Hormonal changes during normal menstrual cycle

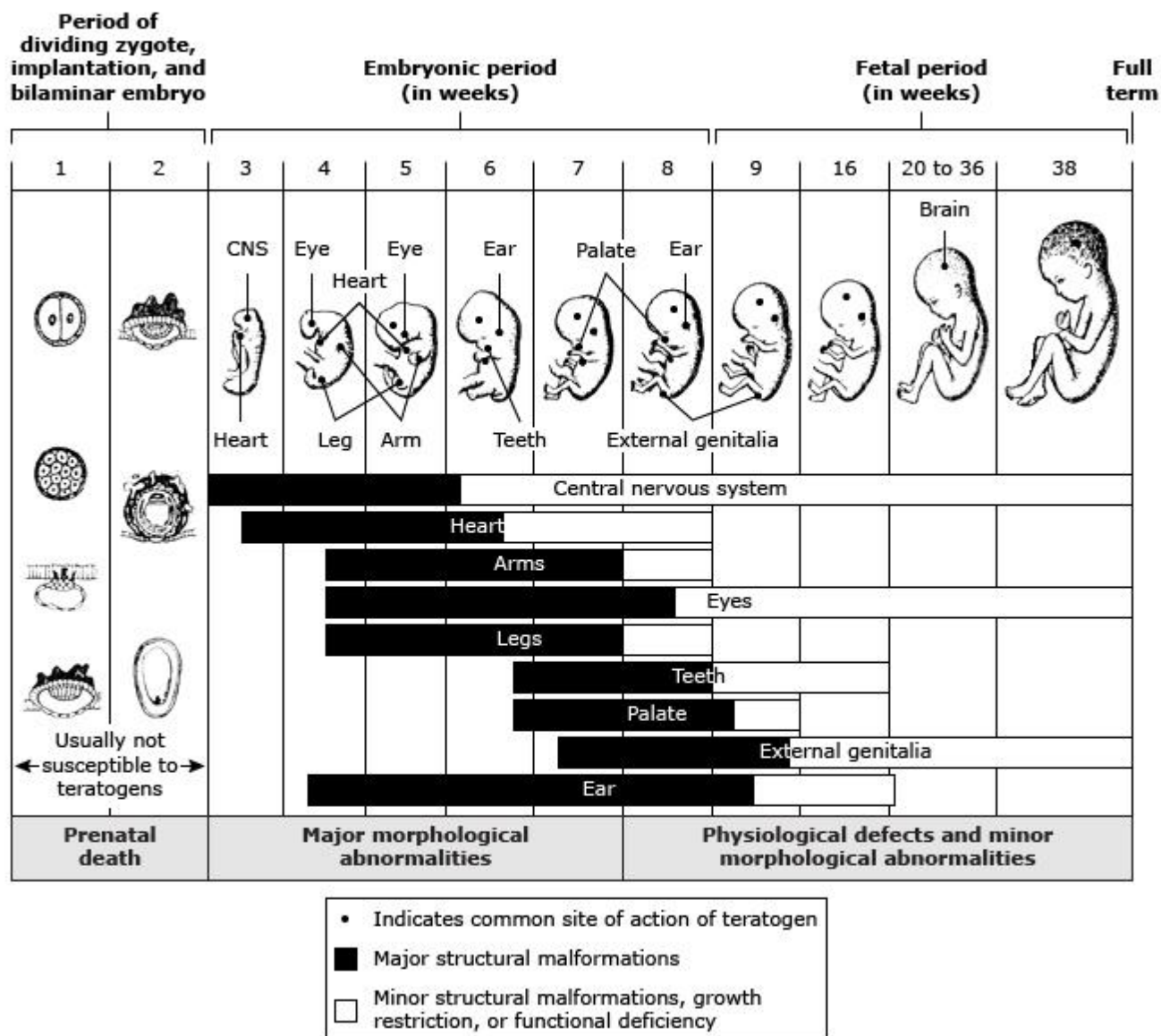


Sequential changes in the serum concentrations of the hormones released from the pituitary gland (FSH and LH; left panel) and from the ovaries (estrogen and progesterone; right panel) during the normal menstrual cycle. By convention, the first day of menses is day 1 of the cycle (shown here as day -14). The cycle is then divided into two phases: the follicular phase is from the onset of menses until ovulation, and the luteal phase is from ovulation until the next menses. To convert serum estradiol values to pmol/L, multiply by 3.67, and to convert serum progesterone values to nmol/L, multiply by 3.18.

LH: luteinizing hormone; IU: international units; FSH: follicle-stimulating hormone.

Graphic 72415 Version 5.0

The developing fetus



The black bars represent the critical period during which development may be disrupted by a teratogen resulting in a major structural malformation. Cell differentiation occurs over a longer period (white bars); exposure during this period can result in minor structural malformations, growth restriction, or functional deficiency. Note, embryonic age is counted from fertilization, whereas menstrual age (ie, gestational age) is counted from the first day of the last menstrual period. Thus, an embryonic age of six weeks corresponds to a menstrual age (gestational age) of eight weeks. Embryonic weeks 1 to 8 are considered the embryonic period of development and are followed by the fetal period of development.

CNS: central nervous system.

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Rose H Goldman, MD, MPH Other Financial Interest: Expert witness [Workers' compensation and disability cases related to occupational medicine and environmental health]. **Blair J Wylie, MD, MPH** Grant/Research/Clinical Trial Support: NIH/NIAID [Obstetrics]; NIEHS [Organophosphate pesticides on pregnancy outcomes]. Consultant/Advisory Boards: Board of Directors of the Society for Maternal-Fetal Medicine [Member]; Pediatric Environmental Health Specialty Network [Obstetrics advisor]. **Louise Wilkins-Haug, MD, PhD** Nothing to disclose **Kristen Eckler, MD, FACOG** Nothing to disclose

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