CHAPTER

TWO

Environments in Reproductive Epidemiology

Learning Objectives

After completing this chapter, you should be able to:

1. Describe how physical, chemical, biological, and psychosocial environments relate to reproductive epidemiology.
2. Describe how the inner versus the outer environments relate to reproductive epidemiology.
3. Describe how personal versus ambient environments relate to reproductive epidemiology.
4. Describe how the solid, liquid, and gaseous environments relate to reproductive epidemiology.
5. Define "systems approach," and describe why it is useful in reproductive epidemiology.
6. Be familiar with selected environmentally related reproductive health problems.

One of the six dimensions of health presented in the previous chapter involves the environment. In a medical sense, the **environment** reflects the aggregate of those external conditions and influences affecting the life and development of an organism.[1] It has also been defined as all that is external to the human host.[2] Epidemiologic research has identified several environments associated with reproductive health. Identifying how selected environments adversely affect reproductive fitness, including sexual behavior, fertility, menstruation, pregnancy outcomes, lactating ability, and sperm count, can enhance strategic thinking and efforts toward mitigating reproductive health problems.

The purpose of this chapter is to consider the full range of existing environments as they relate to reproduction: the physical, chemical, biological, and psychosocial environments; the inner versus outer environment; the personal versus ambient environment; and the solid, liquid, and gaseous environments.

The Physical, Chemical, Biological, and Psychosocial Environments

Exposure to reproductive risk factors before conception may cause reduced fertility, unsuccessful fertilization or implantation, an abnormal fetus, reduced libido, or menstrual dysfunction. Maternal exposure after conception may cause prenatal death, low birth weight, birth defects, developmental or behavioral disabilities, and cancer. A woman may spread a harmful chemical to her child by it crossing the placenta into the growing fetus or by its presence in the fatty breast milk excreted through nursing. For example, alcohol can circulate in the mother's blood, pass through the placenta, and affect the developing fetus. Some reproductive hazards may more directly affect the mother or the fetus such as radiation, which can directly harm a mother's eggs or the fetus.

A number of **physical**, **chemical**, **biological**, and **psychosocial environments** have been associated with adverse reproductive health outcomes (see **Table 2-1**). For example, ionizing radiation can directly harm the developing fetus; some viruses, drugs, and chemicals can influence the health of the mother, which in turn may reduce the supply of nutrients and oxygen to the developing fetus or have a direct influence on the fetus through the mother's blood, and some psychosocial factors such as maternal stress can cause spontaneous abortion or preterm birth.

TABLE 2-1 Environmental Factors That Affect Human Health and Social Well-Being

Physical stresses	Excessive heat, cold, and noise; radiation; vehicular collisions; workplace injuries; and so on
Chemical	Drugs, acids, alkali, heavy metals (lead and mercury), poisons (arsenic), and some enzymes
Biological	Disease-causing infectious agents, pathogens (viruses, bacteria, fungi, parasites)
Psychosocial milieu	Families and households, socioeconomic status, social networks and social support, neighborhoods and communities, formal institutions, and public health policy

Physical

Physical stresses can increase the risk of many reproductive health problems. Physical stresses that increase the risk of spontaneous abortion, for example, include ionizing radiation, noise (>90 dB), heavy physical work, frequent heavy lifting, and prolonged standing. Reduced sperm count is associated with heat and ionizing radiation. Finally, low birth weight is associated with noise (>90 dB), heavy physical work and prolonged standing, and ionizing radiation. Physical factors that can adversely affect paternal and maternal fertility include ionizing radiation and heat.

Noise is a physical stressor that can cause birth defects. In one study involving 132 women working in the metal industry at Valjevo, Serbia, 82 were identified as being exposed to increased noise, while 50 were not in noisy locations. Those working in the noisy environment were significantly more likely to have a miscarriage, low birth weight, and preterm babies.[3] In a case-control study conducted in 29 hospitals in Shanghai, China, with 1,875 perinatal deaths and newborns with birth defects and 1,875 controls, exposure to occupational noise during pregnancy was significantly associated with increased risk of antepartum (predelivery) fetal death.[4] In a prospective study comparing 111 pregnant women exposed to occupational noise with 181 pregnant women with similar work conditions but no noise exposure, researchers discovered that when the noise exposure was at least 90 dB, a decline in birth weight and gestational age resulted.[5]

Different types of radiation create important environments in reproductive health. Ionizing radiation is a physical environment that has sufficient energy to strip away electrons from atoms or to break certain chemical bonds. The fetus is very sensitive to ionizing radiation. Ionizing radiation exposure has been associated with reduced head or brain size, slowed growth, blindness, spina bifida, cleft palate, and mental retardation.[6] Maternal thyroid exposure to diagnostic radiation is associated with a slight reduction in birth weight.[7] Embryo exposure to radio frequency—an extremely low frequency—and intermediate frequency electromagnetic fields has not shown an adverse affect on childhood development.[8]

Scientists estimate that 4 per 1,000 fetuses between 8 and 15 weeks old exposed to 1 REM (a measure of ionizing radiation) will become mentally retarded. Genetic mutation where a parent passes on a genetic error to their child is estimated to occur in about 50 children per million live births when both parents were exposed to 1 REM (Environmental Protection Agency).[9]

Chemical

Some chemicals can adversely influence reproductive fitness, including sexual behavior, fertility, menstruation, pregnancy outcomes, lactating ability, and sperm count. For example, certain cancer treatment drugs can increase the risk of infertility, miscarriage, birth defects, and low birth weight. Certain ethylene glycol ethers such as 2-ethoxyethanol and 2-methoxyethanol can increase the risk of miscarriages. Carbon disulfide can influence menstrual changes, and lead can increase the risk of infertility, miscarriage, low birth weight, and developmental disorders.[10]

The study of adverse effects of chemicals on living organisms is called **toxicology**. The toxic severity of a substance that enters the body is influenced by the route of exposure, duration of exposure, concentration of exposure; rate and amount absorbed; distribution and concentrations within the body, efficiency with which the body changes the substance and the metabolites produced; ability of the substance or metabolites to pass through cell membranes and affect cell components; duration and amount of the substance or metabolites in body tissues; and the rate, amount, and site of departure of the substance or metabolites from the body.

Reproductive toxicology is the occurrence of biologically adverse effects on the reproductive systems of males and females that result from exposure to environmental agents.[11] A related term to reproductive toxicity is developmental toxicity. **Developmental toxicology** is the study of adverse health effects on the developing

organism that result after exposure to chemicals leading to death of the developing organism, structural abnormality, altered growth, or functional deficiency.[12] Adverse health effects may be detected at any point over a person's life span. Developmental toxicity may arise from exposure before conception (in either parent), during prenatal development, or postnatal prior to sexual maturation.[13]

Dioxin is a name given to a class of extremely toxic chemicals that are persistent in the environment and can cause hormone disruption. Dioxin can bind to a cell's hormone receptor, thereby modifying the functioning and genetic mechanism of the cell. A wide range of adverse effects may result from exposure, including miscarriages, birth defects, inability to maintain pregnancy, decreased fertility, reduced sperm counts, endometriosis, learning disabilities, immune system suppression, lowered testosterone levels, nerve and blood disorders, and cancer.

Dioxin literally alters the production and function of many different hormones, growth factors, and enzymes. By changing gene functions, genetic diseases may appear. Even a single dose at a very low concentration of dioxin may seriously disrupt normal reproduction in humans. Hence, there is no "threshold" dose.[14]

Dioxin is formed as an unintentional by-product of many industrial processes by burning chlorine-based chemical compounds with hydrocarbons. Waste-burning incinerators and backyard garbage burning are major sources of dioxin pollution. Other sources include paper mills, the production of polyvinyl chloride (PVC) plastics, and the production of certain chlorinated chemicals (e.g., many pesticides), insecticides, and herbicides (weed killers).[14]

Few people in the population are exposed to high levels of dioxins. When people are exposed to dioxins, it tends to be through their diet. More than 95% of dioxin exposure comes through dietary intake of animal fats. Only a small amount of exposure occurs by breathing air containing trace amounts of dioxins on particles and in vapor form, by inadvertently ingesting soil containing dioxins, or by absorbing it through the skin.[15]

Biological

A number of viruses and other disease-causing (infectious) agents have been shown to adversely affect reproductive health. For example, measles, mumps, and rubella are associated with adverse pregnancy outcomes and fetus development. Evidence of congenital defects of rubella virus infection in early pregnancy is related to congenital defects and, if in the first trimester, increased fetal loss. In

addition, a significant association between maternal mumps in the first trimester and an increased risk of spontaneous abortion has been observed. Measles and rubella (but not mumps) virus infections are linked to an increased premature birth rate. For all three types of infections occurring in late pregnancy, birth of an infected infant can occur.[16]

Infection can be devastating and hard to treat, but risk reduction is possible. Immunity through earlier exposure or vaccinations can generally make a person risk free for diseases such as hepatitis B, human parvovirus B19, rubella, or chicken pox. Pregnant women without prior immunity need to take precautions to avoid exposure to infected individuals. Good hygienic practices are important to reduce the spread of infectious diseases among children in schools and daycare centers and among adults in a myriad of settings. Safe disposal of needles and bodily fluids is also important to protect against infectious agents found in blood and urine.

Psychosocial

Psychosocial factors have also been associated with adverse reproductive outcomes. For example, spontaneous abortion and menstrual disturbances are related to irregular work hours, and spontaneous abortion and preterm birth have been associated with stress. Stress and irregular work hours may also affect fertility and pregnancy in women. For example, preeclampsia is a primary cause of maternal and perinatal morbidity. In a study involving 102 cases of preeclampsia compared with 4,381 controls, physically demanding and stressful occupational conditions were significantly associated with increased risk of preeclampsia. Specifically, women who regularly stood at least 1 hour per day without walking, women who frequently climbed stairs, and women who worked more than 5 consecutive days without a day off experienced significantly higher levels of preeclampsia.[17]

A qualitative summary of the potential effects of selected physical, chemical, biological, and psychosocial environments on the female and male reproductive systems is shown in **Table 2-2** and on paternal and maternal fertility in **Table 2-3**. The information in the tables is taken from three review articles,[18–20] combined by Burdolf and colleagues.[21]

Although the results summarized by the review articles represent well-established exposures and reproductive health outcomes, uncertainties remain. First, much of the exposure assessment involved self-reported questionnaire data. Hence, the accuracy of the magnitude and duration of exposure data may be

TABLE 2-2 Adverse Reproductive Health Outcomes and Their Accompanying Risk Factors

Risk Factor	*Pregnancy Outcomes (Maternal Exposure)*	*Birth Defects (Fetal Exposure)*	*Semen Quality (Paternal Exposure)*
Physical factors			
Ionizing radiation	Spontaneous abortion	Congenital defects	Reduced sperm count (Azoospermia)
Noise (>90 dBA)	Spontaneous abortion, low birth weight, preterm birth		
Heat			Reduced sperm count
Chemical agents			
Lead	Low birth weight	Neural tube defects	Reduced sperm count
Mercury	Spontaneous abortion		
Organic solvents	Spontaneous abortion		
Tetrachloroethylene	Spontaneous abortion	Cleft lip/palate	
Glycol ethers	Spontaneous abortion		Reduced semen quality
Dibromopropane	Menstrual disturbances, spontaneous abortion	Neural tube defects	Reduced semen quality
Ethylene oxide	Preterm birth, spontaneous abortion	Cleft lip/palate	
Anesthetic gases	Spontaneous abortion		
Antineoplastic drugs	Spontaneous abortion		
Pesticides			Reduced sperm count (Azoospermia)
Ethylenedibromide		Neural tube defects, cleft lip/palate	Reduced quantity and quality
Carbon sulfide			Reduced quantity and quality
Specific types of welding			Reduced quantity and quality

(continues)

TABLE 2-2 ***(Continued)***

Risk Factor	*Pregnancy Outcomes (Maternal Exposure)*	*Birth Defects (Fetal Exposure)*	*Semen Quality (Paternal Exposure)*
Psychosocial factors			
Irregular work hours	Spontaneous abortion, menstrual disturbances		
Stress	Spontaneous abortion, preterm birth		
Physical load			
Heavy physical work (high energy expenditure)	Spontaneous abortion, low birth weight		
Frequent heavy lifting	Preterm birth, spontaneous abortion		
Prolonged standing	Low birth weight, preterm birth, spontaneous abortion		

Source: Burdolf A, Figa-Talamanca I, Jensen TK, Thulstrup AM. Effects of occupational exposure on the reproductive system: core evidence and practical implications. *Occup Med* 2006;56(8):516–520.

biased. In addition, because many of the individuals in these studies were exposed to a mixture of exposures, it is difficult to differential the risk of specific chemical compounds. Second, whether the appropriate time window was used for exposure assessment may be questioned. For many occupational hazards, the appropriate time window for greatest susceptibility is not well known. Third, changes in chemical exposures over time complicate determination of the dose. Finally, it is difficult to attribute paternal exposure to an adverse health outcome when there is overlapping exposure between partners.[21]

Observed health effects associated with selected pathological agents are presented in **Table 2-4**. The table also shows potentially high risk occupations and prevention measures. Adverse reproductive effects in pregnant women may also occur from infectious agents. For example, human cytomegalovirus (CMV) is the leading cause of congenital viral infections in the United States, involving 1% to 3% of live births.[22] Congenital CMV infection is as common as neural tube

TABLE 2-3 Fertility Outcomes and Their Accompanying Risk Factors

Occupational Risk Factor	*Maternal Exposure*	*Paternal Exposure*
Physical factors		
Ionizing radiation	+	+
Heat	+	+
Chemical agents		
Lead	+	+
Mercury	+	
Toluene	+	
Aliphatic hydrocarbons	+	
Aromatic hydrocarbons	+	
Tetrachloroethylene	+	
Glycol ethers	+	+
Ethylene oxide	+	
Anesthetic gases	+	
Pesticides	+	+
Psychosocial factors		
Irregular work hours	+	
Stress	+	

Source: Burdolf A, Figa-Talamanca I, Jensen TK, Thulstrup AM. Effects of occupational exposure on the reproductive system: core evidence and practical implications. *Occup Med* 2006;56(8):516–520.

defects, fetal alcohol syndrome, and Down syndrome.[23] In the United States, about 40,000 infants are born each year with CMV, of which 8,000 will have neurological disabilities, including mental retardation, neuromotor abnormalities, hearing loss, and chorioretinitis.[24] Maternal CMV infection during gestation is related to a 40% risk of intrauterine transmission, with roughly a quarter of these infants symptomatic.[25,26] One study showed that women treated with hyperimmunoglobulin who have primary maternal CMV infection and whose fetuses were infected gave birth to significantly fewer symptomatic infants than did women who were not treated.[27]

As for birth defects, research has linked them with rubella (German measles), cytomegalovirus, and herpes simplex; untreated syphilis in the mother; and the parasite *Toxoplasma gondii* that can be contracted through undercooked meat, dirt, or feces of infected cats.

TABLE 2-4 Disease-Causing Agents That Are Reproductive Hazards for Women

Agent	*Observed Effects*	*Potentially Exposed Workers*	*Preventive Measures*
Cytomegalovirus	Birth defects, low birth weight, developmental disorders	Healthcare workers, workers in contact with infants and children	Good hygienic practices such as hand washing
Hepatitis B virus	Low birth weight	Healthcare workers	Vaccination
HIV	Low birth weight, childhood cancer	Healthcare workers	Practice universal precautions
Human parvovirus B19	Spontaneous abortion	Healthcare workers, workers in contact with infants and children	Good hygienic practices such as hand washing
Rubella (German measles)	Birth defects, low birth weight	Healthcare workers, workers in contact with infants and children	Vaccination before pregnancy if no prior immunity
Toxoplasmosis	Spontaneous abortion, birth defects, developmental disorders	Animal care workers, veterinarians	Good hygiene practices such as hand washing
Varicella-zoster virus (chicken pox)	Birth defects, low birth weight	Healthcare workers, workers in contact with infants and children	Vaccination before pregnancy if no prior immunity

Source: National Institute for Occupational Safety and Health. The effects of workplace hazards on female reproductive health. DHHS (NIOSH) Publication No. 99-104, 1999.

The Inner Versus Outer Environment

The inner environment with respect to the body is compared with the outer environment; that is, harmful substances in the outer environment enter the body through various routes, for example, breathing in (inhalation), swallowing (ingestion), contact with skin, and intravenous. The body has protective mechanisms for

contaminants that penetrate these barriers, such as vomiting, diarrhea, detoxification in the liver, excretion through the kidneys, and coughing. A substance is considered to be outside the body until it crosses cellular barriers in the gastrointestinal tract or lungs. Cell membranes (cell walls) are designed to prevent forcing invaders or substances from entering bodily tissue. If a toxic substance is absorbed in the body, it can be distributed to other sites through blood and lymph circulation, liver, kidneys, and lungs.

Once a toxicant passes the lining of the skin, lungs, or gastrointestinal tract, it enters fluid surrounding the cells of that organ (interstitial fluid). Interstitial fluid represents about 15% of body weight. Fluid inside the cells is called intracellular fluid and represents about 40% of body weight. A toxicant in the interstitial fluid can enter cells of local tissue, blood capillaries and the body's circulatory system, or the lymphatic system. A toxicant can then be excreted (through feces, urine, or expired air), stored, or biotransformed into metabolites.

Biotransformation is transformation of a substance into new chemicals (metabolites) by the body. Biotransformation is essential for survival. For example, it involves transforming absorbed nutrients (food, oxygen, etc.) into substances required by the body for normal function. In addition, the body is efficient at biotransforming body wastes or chemicals that are not normally produced or expected in the body. Water-soluble metabolites, which are excreted into bile and passed from the body, may result. Metabolizing a substance to a lower toxicity is called detoxification; however, metabolites may become more toxic (bioactivation). An interaction of metabolites with cellular macromolecules such as DNA can cause serious health effects such as birth defects.

A highly toxic substance that is poorly absorbed into the body may be less dangerous than a substance with low toxicity but which is readily absorbed in the body.

A mutation may arise if genes that govern cell division and cell suicide (apoptosis) are damaged and cannot be repaired. Although the body may fail to repair damaged genes, the process of trying to repair genes may also create mutations. In some cases, the body can repair damaged tissue, but sometimes the damage cannot be repaired, or it may be too widespread and severe to be repaired.

When a gene is damaged, it will no longer properly guide how the body forms and functions. Genes control all aspects of the human body. They are influenced by both radiation and chemicals. Sometimes genes mutate at random, without any explanation. We inherit tens of thousands of genes from each parent, which are arranged on 46 chromosomes. Half of our genes come from our mother

and half come from our father. For each pair of genes, one will dominate, while the other is recessive, thereby determining each characteristic. Several birth defects result from dominant inheritance (e.g., high cholesterol, Huntington's disease, nervous system disorders, and some forms of glaucoma).

If both the mother and father have the same recessive gene, the child has a 25% chance of inheriting the disease. Some recessive diseases include sickle cell anemia, cystic fibrosis, and phenylketonuria (PKU), a metabolic disorder. If only one parent passes on genes for the disorder, a normal gene received from the other parent will prevent the disease; however, the child will be a carrier.

Some disorders, like hemophilia and Duchenne muscular dystrophy, occur when defective sex-determining chromosomes carried on the X chromosome are passed on by the parent. A defective egg or sperm can also result in genetic defects (e.g., Down syndrome).

The complicated interaction of genes from either or both parents with environmental factors is thought to explain a host of defects: cleft lip and palate, clubfoot, spina bifida, water on the brain (hydrocephalus), diabetes mellitus, heart defects, and some cancers.

Birth defects have also been linked to diseases in the mother. For example, children of diabetic mothers are significantly more likely to experience cardiovascular malformations.[29] In one study, maternal obesity was significantly associated with spina bifida.[30] The study also found a significant positive association between infants of obese women and omphalocele (a type of hernia), heart defects, and multiple anomalies, and heart defects and multiple anomalies in overweight women prior to pregnancy. Neural tube defects (i.e., defects of the fetal brain or spine) have also been associated with maternal obesity prior to pregnancy;[31] however, another study did not find a significant association between maternal obesity and spina bifida.[32]

The Personal Versus Ambient Environment

The **personal environment** where an individual has control (e.g., diet, smoking, and sexual behavior) may be contrasted with the **ambient environment** where a person has little or no control (e.g., food additives, pollution, and industrial products). Many events and environments in reproductive health may be classified as personal in some situations and ambient in others. For example, we may or may not have control over family planning, skilled attendance at delivery, and timely

emergency obstetric care when complications arise, which are important ways to avoid reproductive health problems.

Both personal and ambient environments may cause mutations. Congenital malformations can be genetic or teratogenic. Environmental agents may disrupt the reproductive process by affecting genetic material (DNA or chromosomes) or by directly disturbing the developing embryo or fetus.

If an environmental agent changes DNA, it is **mutagenic**. Relevant exposures should be studied before pregnancy, when the gametes are formed or, more specifically, during the formation of the meiotic divisions. Meiotic divisions leading to the development of sperm cells in men occur 3 months before conception. Eggs enter their first meiotic division during fetal life in women. Eggs remain at this stage until the menstrual cycle, decades later. At that time, it matures and may get fertilized;[33] however, there are many difficulties in identifying environmental agents that increase mutagenic events in gametes. In the study of environmental agents that may cause birth defects and other reproductive problems, environmental exposures affecting both parents in the years or decades before conception should be considered.

When a developing embryo or fetus is exposed to an environmental agent, it is very unlikely that a birth defect will result. Rather, somatic cell mutations (any cell in the body that is not a sperm or egg cell) in developing tissue are more likely to result in congenital, childhood, or adolescent cancers.

A **teratogen** is any environmental exposure that may cause disturbances of the growth and development of an embryo or fetus, causing birth defects. Thus, exposures to pregnant women are of interest. Exposures to men are only of interest when they secondarily affect women (e.g., passive smoke, occupational chemicals carried home, or biological agents). **Teratology** is the study of the frequency, causation, and development of congenital malformations such as morphological abnormalities (e.g., cleft lip and/or palate, anencephaly, or ventricular septal defect) and other phenomena (e.g., increased risk of cancer). The American College of Occupational and Environmental Medicine recognizes the following teratogens:

- Ionizing radiation: atomic weapons, radioiodine, radiation therapy
- Infections: cytomegalovirus, herpes virus hominis I and II, parvovirus B-19, rubella virus (German measles), syphilis, toxoplasmosis, Venezuelan equine encephalitis virus

- Metabolic imbalance: alcoholism, endemic cretinism, diabetes, folic acid deficiency, hyperthermia, phenylketonuria, rheumatic disease and congenital heart block, virilizing tumors
- Drugs and environmental chemicals: 13-cis-retinoic acid (isotretinoin, Accutane), aminopterin and methylaminopterin, androgenic hormones, busulfan, captopril and enalapril (ACE inhibitors), chlorobiphenyls (PCBs), cocaine, coumarin anticoagulants, cyclophosphamide, diethylstilbestrol, diphenylhydantoin (Phenytoin, Dilantin, Epanutin), etretinate, lithium, methimazole, organic mercury compounds, penicillamine, tetracyclines, thalidomide, trimethadione, and valproic acid[34]

Teratogenesis causing specific malformations may occur in limited periods of development, depending on the specific teratogenic process. If a malformation results, the teratogenic period corresponds to when the structure in question is developing. Embryonic timetables may provide very crude estimates of periods of sensitivity.

Although some of these teratogens cannot be controlled, many can. Some infections are sexually transmitted. Some sexually transmitted diseases (STDs) include chlamydia, gonorrhea, hepatitis B, and syphilis. STDs may cause cervical and other cancers, chronic hepatitis, pelvic inflammatory disease, infertility, and other complications, as well as pregnancy complications (e.g., premature labor and uterine infection after delivery).[35] Chlamydia has been linked with male reproductive tract complications such as prostatitis, infertility, and urethral stricture.[36] STDs can also cause problems and be passed to the baby both while in the womb or during birth. The effects of STDs on the baby include stillbirth, neurological damage, meningitis, low birth weight, and possible lifelong STD complications.[35]

Another STD and condition strongly related to reproductive health is HIV/AIDS. This is in itself a reproductive health problem as well as a major contributor to other reproductive health problems. The primary mode of transmission is through sexual contact and from mother to child during childbirth, thus making it a reproductive issue. HIV/AIDS also causes other reproductive problems such as erectile dysfunction,[37] ectopic pregnancy, bacterial pneumonia, urinary tract infections, and other infections in HIV-positive as compared with HIV-negative pregnant women.[38] HIV-positive women also experience lower fertility rate ratios, more postpartum hemorrhaging, a higher risk of major and minor complications

after caesarean sections, and a higher risk of both major and minor complications with laparotomy, caesarean section, and induced abortion.[38]

Pregnant women also have control over whether they drink during pregnancy, take illicit drugs, or abuse prescription drugs. If large amounts of alcohol are consumed during pregnancy, a cluster of defects called fetal alcohol syndrome may arise, such as mental retardation, attention-deficit hyperactivity disorder, language deficits, deficits in spatial processing and memory, slow reaction times, decision-making problems, heart problems, and growth deficiency.[39] Binge drinking in early pregnancy has also been shown to be dangerous, even if the woman quits drinking later. There is no safe time during pregnancy to drink. An estimated 1% of all births in the United States are estimated to have some form of fetal alcohol syndrome.[39]

Recreational drug use and abuse of prescription drugs is also a choice. Some drugs like d-lysergic acid diethylamide (LSD) can cause arm and leg abnormalities and central nervous system problems in infants. Crack cocaine also has been associated with birth defects. In the United States in 2002, 3% of pregnant women aged 15 to 44 years used illicit drugs in the past month, and 3% reported binge alcohol drinking. Pregnant women aged 15 to 25 years were more likely to use illicit drugs and binge drink than older pregnant women.[40] Several drugs prescribed for anxiety and mental illness are known to cause specific defects. In the United States in 2002–2004 among women aged 15–44, 6% of pregnant women reported nonmedical use of any prescription drug, pain relievers, stimulants, methamphetamine, and sedatives in the past year.[41]

Drugs taken to treat other health problems may cause damage to a developing fetus as well. For example, certain antibiotics can harm bone growth. Drugs used to treat tuberculosis can cause hearing problems and cranial damage. Drugs given to prevent seizures can cause mental retardation and slow growth. Drugs given to treat cancer can cause congenital malformations, especially central nervous system defects, and male hormones may cause masculinization of a female fetus.[42]

The Solid, Liquid, and Gaseous Environments

Routes of human exposure to contaminants that may cause reproductive health problems are becoming better understood. Transmission of chemical (e.g., carbon monoxide, ozone, and lead) and biological agents (viruses, bacteria, funguses, and parasites) often occurs through air, water, soil, and food. An understanding of

how chemical and biological agents can be transmitted is important in avoiding exposure.

On the basis of understanding selected routes of transmission, the National Institute for Occupational Safety and Health recommends the following measures for avoiding hazardous chemical exposure in the workplace:

- Store chemicals in sealed containers when they are not in use.
- Wash hands after contact with hazardous substances and before eating, drinking, or smoking.
- Avoid skin contact with chemicals.
- If chemicals contact the skin, follow the directions for washing in the material safety data sheet (MSDS). Employers are required to have copies of MSDSs for all hazardous materials used in their workplaces and to provide them to workers upon request.
- Review all MSDSs to become familiar with any reproductive hazards used in your workplace. If you are concerned about reproductive hazards in the workplace, consult your doctor or healthcare provider.
- Participate in all safety and health education, training, and monitoring programs offered by your employer.
- Learn about proper work practices and engineering controls (such as improved ventilation).
- Use personal protective equipment (gloves, respirators, and personal protective clothing) to reduce exposures to workplace hazards.
- Follow your employer's safety and health work practices and procedures to prevent exposures to reproductive hazards.
- Prevent home contamination with the following steps:
  - Change out of contaminated clothing and wash with soap and water before going home.
  - Store street clothes in a separate area of the workplace to prevent contamination.
  - Wash work clothing separately from other laundry (at work if possible).
  - Avoid bringing contaminated clothing or other objects home. If work clothes must be brought home, transport them in a sealed plastic bag.[28]

In order to avoid viruses and other infectious agents, follow precautionary practices such as those indicated in Table 2-3. These include good hygienic practices such as hand washing, vaccination before pregnancy if there is no prior immunity, and precautions against HIV.

Certain activities are associated with increased exposure to the chemical and physical agents that cause reproductive problems. For example, healthcare workers and pharmacists are more likely to be exposed to cancer treatment drugs; electronic and semiconductor workers are more likely exposed to certain ethylene glycol ethers; battery makers, solderers, welders, radiator repairers, bridge repainters, firing range workers, and home remodelers are more likely to be exposed to lead; healthcare workers, dental personnel, and atomic workers are more likely exposed to ionizing radiation; and many types of workers experience strenuous physical labor.

Broadly speaking, the study of reproductive epidemiology requires consideration of all of these types of environments and their interrelationships. That is, environmental factors that adversely affect reproductive health should be recognized and understood in terms of how they may become internalized, whether they can be controlled, and the routes of human exposure they might take. The study of the environment may be restricted by person (e.g., adolescent girls), place (e.g., workplace), or time (e.g., summer) and environments that can be modified. Reproductive health interventions may modify physical, biological, chemical, and psychosocial environments and corresponding behaviors (e.g., exercise, diet, sexual practices).

The Systems Approach

A **systems approach** is a comprehensive assessment in which the health problem is related to the complexity of environmental exposures, with consideration given to the interrelated, interacting, or interdependent constituents forming a complex whole. Consideration is given to the fact that environmental exposures may derive from multiple sources, enter the body through multiple routes, and change over time because of constant interaction, altering the degree to which they are harmful. The essence of the systems approach is to understand the source and nature of an environmental contaminant or stress capable of influencing reproductive behavior, assessing how and in what form it influences people, measuring the reproductive health effects, and applying controls when and where appropriate.

This approach often requires the combined efforts of epidemiologists, biologists, toxicologists, respiratory physiologists, and public health officials.

In the context of reproductive health, a systems approach is a comprehensive assessment in which the reproductive health problem is related to the complexity of environmental exposures, with consideration given to the interrelated, interacting, or interdependent constituents forming a complex whole. Consideration of all the definitions of environment presented above is important in the study, prevention, and control of reproductive health problems.

Selected Reproductive Health Outcomes

Menstrual Cycle Effects

Physical or emotional stress or chemical exposure may disrupt the balance between the brain, pituitary glands, and ovaries. Consequently, an imbalance of estrogen and progesterone may result, leading to changes in menstrual cycle length and regularity and ovulation. Overall female health is associated with severe or long-lasting hormone imbalances. Carbon disulfide (CS_2) has been shown to cause menstrual cycle changes among viscose rayon workers.

Infertility and Subfertility

The capability to conceive is sometimes called **fecundity**. The capability to produce live children is termed **fertility**. Environmental hazards to reproduction as well as problems with either the male or female reproductive systems can affect fecundity and fertility. Lack of fertility is referred to as **infertility**, and permanent infertility is termed **sterility**. **Subfertile** is a level of fertility below the normal range, but not infertile. Many factors influence human fecundity and fertility, including genetics, nutrition, physical activity, sexual behavior, endocrinology, timing, culture, and instinct.

Various factors can affect fertility and may involve one or both partners. For example, smoking and alcohol use in males are associated with fewer sperm and poor semen quality.[43] Long-term cigarette smoking has been associated with increased risk of erectile dysfunction.[44] Excessive weight has been associated with lower sperm concentration, total sperm count, and fewer normal forms.[45] Obesity increases the risk of infertility and abnormal or irregular anovulation and reduced response to fertility treatment in women,[46] and cancer, independent of treatment, has been shown to disrupt spermatogenesis.[47]

Between 10% and 15% of all couples cannot conceive a child after 1 year of attempting to become pregnant. Factors that can cause problems with fertility include damage to a man's sperm, damage to a woman's eggs, or a change in the hormones that regulate the normal menstrual cycle. Certain cancer treatment drugs (e.g., methotrexate), lead, and ionizing radiation (e.g., X-rays and gamma rays) are examples of risk factors for infertility/subfertility.[48]

Miscarriage and Stillbirths

Miscarriage (also called spontaneous abortion) is the death and expulsion of an embryo or a fetus; it is an unplanned termination of a pregnancy. It may occur any time after conception and before 20 weeks of gestation.[49,50] Studies reveal that anywhere from 10% to 25% of all clinically recognized pregnancies will end in miscarriage.[51] A **stillbirth** occurs when the fetus, which died in the uterus or during labor or delivery, exits the woman's body. Some of the reasons why miscarriages and stillbirths occur are as follows:

- Damage to the egg or sperm such that the egg cannot be fertilized or that it cannot survive after fertilization.
- The hormone system may not work properly to maintain the pregnancy.
- The fetus may develop abnormally.
- The uterus or cervix may have physical problems.

The cause of miscarriage is often difficult to identify; nevertheless, during the first trimester, the majority of miscarriages have gross chromosomal anomalies.[52] Examples of known risk factors for miscarriage include hormonal problems, infections or maternal health problems, obesity, lifestyle (e.g., drug use, malnutrition, and smoking, maternal age, cancer treatment drugs), certain ethylene glycol ethers, lead, ionizing radiation, and strenuous physical labor (e.g., prolonged standing, heavy lifting). In addition, embryonic development may be normal, but is rejected by the maternal organism.

Birth Defects

In the United States, about 150,000 babies (i.e., approximately 3%, or 1 in 30) are born with a birth defect, with the cause of 60% to 70% of birth defects unknown.[53] A **birth defect** is a structural, functional, or developmental abnormality present

at birth or later in life. In the previous chapter, mutagenic effects and teratogenic effects were identified as environmental causes of birth defects. The fetus is most susceptible to adverse effects during the first 3 months of the pregnancy when the internal organs and limbs are formed. Cancer treatment drugs, lead, and ionizing radiation are examples of risk factors for birth defects.

Birth defects develop from both genetic and environmental factors. A single abnormal gene is sufficient to cause birth defects. Humans have at least 30,000 to 35,000 genes that direct the development of our physical and biochemical systems. A chromosome is a single piece of DNA that contains many genes. The average human cell has 46 chromosomes. Because each child gets half of its genes from each parent, an infant may inherit a genetic disease when either parent passes on a single faulty gene, which is called **dominant inheritance**. Achondroplasia (a form of dwarfism) and Marfan syndrome (a connective tissue disease) are examples of dominant inheritance. Other genetic diseases can only be passed on to a child if both parents carry the same abnormal gene, which is called **recessive inheritance**. An example is cystic fibrosis, which is a fatal disorder of lungs and other organs. This disease tends to affect mainly Caucasians. In addition, there is a form of inheritance (X-linked) in which a mother who carries a gene can pass it to her son. This form of inherited disease includes hemophilia (a blood-clotting disorder) and Duchenne muscular dystrophy (progressive muscle weakness).[54]

Numerous birth defects are possible. Error in the development of an egg or sperm cell may cause a baby to be born with too many or too few chromosomes. One or more chromosomes may be broken or rearranged. An extra chromosome 21 (Down syndrome) is a more common chromosomal abnormality. Infants born with extra copies of chromosome 13 or 18 have multiple birth defects. These children do not usually live beyond the first month of life. Extra or missing sex chromosomes can affect sexual development and cause infertility, growth abnormalities, and learning and behavioral problems, but most affected people have normal lives.[54]

Although the association between maternal age and the risk of birth defects has been extensively studied, research has also examined the relationship between paternal age and risk of birth defects. Infants born to younger or older fathers have a slightly increased risk of birth defects; nevertheless, compared with mothers, paternal age plays a smaller role in the etiology of birth defects.[55]

Environmental factors can also result in birth defects, including biological and chemical agents. Although the causes of most birth defects are currently

unknown, some teratogens a pregnant women may put into her system that may affect the fetus include *alcohol*, associated with mental retardation, low birth weight, heart defects, poor coordination, and selected malformations; *tobacco*, associated with reduced oxygen available to the fetus, premature rupture of the membranes, hemorrhage before or early in labor, hemorrhage after delivery, congenital abnormality, miscarriage, stillbirth, premature birth, and low birth weight; *caffeine*, which is a stimulant that acts on the nervous system, creating changes in fetal heartbeat and other functions; *aspirin*, which may increase the risk of anemia, excessive bleeding before and after birth, longer pregnancies, and higher frequency of complicated deliveries; *barbiturates*, which can cause the baby to experience tremors, restlessness, and irritability; *amphetamines*, which can cause birth defects; *antibiotics*, which may affect the growth of the baby's bones or yellow mottling and staining of the baby's first teeth and deafness in the infant; *narcotics*, which result in fetal addiction to the drug and an increased risk of premature birth, breach birth, toxemia, and premature separation of the placenta; and hallucinogens, which can affect the central nervous system of the fetus. If a birth defect is caused by a combination of one or more genes and environmental factors, it is called multifactorial inheritance. Examples are cleft lip or palate, clubfoot, and some forms of heart defects.

Just as defects may arise in any organ or part of the body, the severity of the disturbance can vary considerably. Consider a neural tube defect, which occurs in human embryos if there is an interference with the closure of the neural tube around the 28th day after fertilization. Researchers have identified some causes for this condition, including medication for epilepsy taken during pregnancy, folic acid deficiencies, folate antimetabolites, maternal diabetes, maternal obesity, mycotoxins in contaminated cornmeal, arsenic, and hyperthermia during early development.[56] The types of neural tube defects range from spina bifida (incompletely formed spinal cord), encephalocele (sac-like protrusions of the brain and the membranes that cover it through openings in the skull), and anencephaly (absence of a major portion of the brain, skull, and scalp).

In the United States, birth defects surveillance systems historically have collected data on major structural birth defects and birth defects arising from chromosomal abnormalities. Major structural birth defects are conditions that (1) result from a malformation, deformation, or disruption in one or more parts of the body; (2) are present at birth; and (3) have a serious, adverse effect on health, development, or functional ability. The most common type of structural birth defect involves the heart, which affects one in every 125 babies. About 1 in 2,000 babies

will experience spinal bifida, which results in varying degrees of paralysis and bladder and bowel problems. Genetic and nutritional factors appear to affect this defect. Metabolic disorders affect 1 in 3,500 babies. Affected infants are missing an enzyme necessary to break down certain fatty substances in brain cells. As these substances build up, brain cells are destroyed. Consequences of this defect are blindness, paralysis, and death by age 5. In addition, roughly 1 in 135 infants will have a structural defect involving the genitals or urinary tract, varying in severity and form.

Congenital infections are also causes of birth defects. For example, if rubella (German measles) infects a pregnant woman during the first trimester, the child has a one in four chance of an outcome of congenital rubella syndrome (deafness, mental retardation, heart defects, or blindness). Vaccination for rubella has now made congenital rubella syndrome rare. Cytomegalovirus is the most common congenital viral infection. In the United States, although roughly 1% of infants are infected, only about 10% of them experience adverse health outcomes such as mental retardation and low vision or hearing. Finally, sexually transmitted infections can endanger the fetus and newborn. For example, if syphilis is untreated it can cause stillbirth, newborn death, or bone defects. Sexually transmitted infections affect about 1 in 2,000 babies.[54]

Fetal alcohol syndrome (mental and physical birth defects) affects 1 in 1,000 babies in the United States. It is common in mothers who drink heavily during pregnancy; however, even moderate or light drinking can be dangerous to the developing fetus.[54]

Rhesus incompatibility disease (Rh disease) in an infant is caused by incompatibility between a mother's blood and that of her fetus, which can cause jaundice, anemia, brain damage, and death in the infant. Prevention of Rh disease is possible by injection of immunoglobulin at 28 weeks of pregnancy after the delivery of an Rh-positive infant.[54]

Low Birth Weight and Premature Birth

Low birth weight is when the birth weight is less than 2,500 grams (about 5 pounds, 5 ounces). Premature birth (also called preterm birth) is when childbirth occurs earlier than 37 completed weeks of gestation. In the United States, approximately 7% of babies are born underweight or prematurely. Most of these cases are believed to be because of poor maternal nutrition, smoking, and alcohol use during pregnancy. For example, in the United States, cigarette smoking during pregnancy

explains 20% to 30% of low birth weight babies, about 14% of preterm deliveries, and 10% of infant deaths. Cigarette smoking causes these problems by depriving the fetus of up to 25% of necessary oxygen.[57]

Underweight or premature babies have a greater risk of illness and death during the first year of life. They also have an increased risk of long-term disabilities, such as mental retardation, chronic respiratory problems, cerebral palsy, childhood psychiatric disorders, autism, and hearing and vision impairments. Cancer treatment drugs, lead, ionizing radiation, and strenuous physical labor are examples of risk factors for low birth weight and premature delivery.

In 2004, 12.5% of all births in the United States occurred before 37 weeks gestation (preterm). Premature births are on the rise, increasing 30% since 1981.[58] Roughly two thirds of the increase in premature births are late preterm (born within 34 and 36 weeks of gestation).[59] Mortality rates for late preterm infants are also higher than those born at term.[60–68] All preterm infants have higher morbidity compared with term neonates.[69]

Young and old maternal age at pregnancy has been shown to increase the risk of preterm delivery, low birth weight, and subsequent risk of death and developmental problems.[70–73] Low birth weight infants have greater than six times the risk of infant mortality and are at increased risk of long-term disabilities. **Table 2-5** shows the relationship between low birth weight and maternal age at pregnancy for California in 2006.[74]

TABLE 2-5 Maternal Age at Pregnancy and Low Birth Weight (<2,500 Grams)

Maternal Age Group (Years)	*Percentage*
Under 15	8.9
15–19	7.4
20–24	6.2
25–29	6.1
30–34	6.7
35–39	7.9
40–44	10.2
45 and older	24.4

Data Source: California Department of Public Health. Center for Health Statistics, Vital Statistics Query System. Available at: http://www.applications.dhs.ca.gov/vsq/default.asp. Accessed December 30, 2008.

Developmental Disorders

Sometimes prenatal and postnatal events occur to disrupt cognitive, language, motor, or social skills. Developmental disorder involves one of many disorders that interrupt development in children. A single area of development may be affected or developmental disorders may be pervasive. In the United States, roughly 10% of children have some form of developmental disability (e.g., mental retardation or intellectual disability, autistic disorder, learning disorder, attention deficit hyperactivity disorder, cerebral palsy, vision impairment, and hearing loss). Such problems may not be noticeable at birth, can be difficult to measure, may be temporary, and can reflect a wide range of severity. Lead and ionizing radiation are examples of risk factors for developmental disorders.[75]

Maternal tobacco use during pregnancy has also been shown to have an association with later conduct disorders.[76]

Childhood Cancer

A number of studies are examining suspected or possible risk factors for childhood cancers. These include parental, fetal, or childhood exposures to environmental toxins such as pesticides, solvents, or other household chemicals; parental occupational exposures to radiation or chemicals; parental medical conditions during pregnancy or before conception; maternal diet during pregnancy; and maternal reproductive history. For example, diethylstilbestrol diphosphate is a synthetic (manufactured) form of the female hormone estrogen. In the 1950s and 1960s, it was prescribed to millions of women to prevent miscarriage and premature birth. Its use was discontinued in the 1970s because reproductive abnormalities were found in some of the children of women who took the drug. Prenatal exposure to diethylstilbestrol has also been associated with shown increased risk for cervical and vaginal cancers in female offspring, most often detected in the age range of 14 to 25 years.[77]

The most likely explanation connecting prenatal exposure and cancer is the occurrence of somatic mutations in the fetal cells. This is the mechanism that explains mutations because of prenatal X-rays and possibly chemical carcinogenesis. X-rays and specific genetic syndromes have been associated with leukemia Studies have also associated childhood leukemia with paternal exposure to solvents and paints, and employment in motor vehicle–related jobs, and cancer of the childhood nervous system was associated with paternal exposure to paints.[78] In a

large study conducted in the United Kingdom, small but statistically increased risks of leukemia and acute lymphoblastic leukemia were observed in children whose fathers were exposed to exhaust fumes, driving, and/or inhaled particulate hydrocarbons.[79,80]

Genetic susceptibility may be a risk factor for Hodgkin's disease. Similarly, a retinoblastoma gene has been identified, with each child of a parent with familial bilateral retinoblastoma having a 50% risk of inheriting the gene.

In a study involving hospitals in the United States and Canada, maternal exposures to selected chemicals were not associated with neuroblastoma. On the other hand, paternal exposures to selected chemicals (i.e., diesel fuel, lacquer thinner, turpentine, wood dust, and solders) showed evidence of increased risk of neuroblastoma.[81]

Conclusion

This chapter presented how various environments affect reproductive health. Focus was given to how physical, chemical, biological, and psychosocial environments influence reproductive health; how exposures can penetrate protective mechanisms in the body to adversely affect reproductive health; how a large portion of environmental exposures that influence human reproduction may harm reproductive health; and how an understanding of the routes of exposure to environmental influences can help prevent and control reproductive health problems. By understanding the full range that environments can have on reproductive health, health and social conditions of people may improve.

Key Issues

1. An important part of reproductive epidemiology involves identifying whether the cause of a health-related state or event is the physical, chemical, biological, or psychosocial environment; how a substance can penetrate protective mechanisms in the body; whether a person has control over the environmental exposure; and the routes of human exposure.
2. Reproductive health–related states or events can be caused by substances from the outer environment that enter through inhalation, ingestion, skin contact, or intravenous means or from the inner environment found already within the body (e.g., damaged genes).

3. Reproductive health–related states of events can be caused by factors in the personal environment (within a person's control) and in the ambient environment (where a person has little or no control).
4. Pathologic agents can be transmitted to humans in solid, liquid, and gaseous environments. Understanding how agents can be transmitted is important in avoiding exposure.
5. The systems approach in reproductive epidemiology considers the fact that environmental exposures may derive from multiple sources, enter the body through multiple routes, and that elements in the environment can change over time because of constant interaction, altering the degree to which they are harmful.

Exercises

Key Terms

Define the following terms.

Ambient environment
Biological environment
Biotransformation
Birth defect
Chemical environment
Developmental toxicology
Dioxin
Dominant inheritance
Environment
Fecundity
Fertility
Infertile
Miscarriage
Personal environment
Physical environment
Psychosocial environment
Recessive inheritance
Reproductive toxicology
Sterility
Stillbirth
Subfertile
Systems approach
Teratogen
Teratology
Toxicology

Study Questions

2.1 Identify and discuss routes of human exposure in the environment.

2.2 Give an example of each of the following environments and how each can affect reproductive health outcomes: physical, chemical, biological, and psychosocial.

2.3 Discuss the difference between the inner environment and the outer environment.
2.4 Discuss the difference between a teratogen and a genetic factor. Why would it be important to know the difference?
2.5 Describe the difference between the personal and the ambient environment, and give examples of both.
2.6 Identify some of the high–risk occupations for environmental exposures, and discuss some of the precautions that can be taken to reduce risk.
2.7 Define and discuss three reproductive problems and identify a risk factor for each.

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