12 Evaluation of Occupational Exposures and Effects on Male and Female Reproduction

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A couple's reproductive success and the health of their offspring may be influenced by their environment in ways that are well-established and likely in some ways that may not yet be fully understood or known. The workplace is prominent in most couples' daily environment during their reproductive years. In the United States, 94% of men and 66% of women who are married and between the ages of 20 and 35 years are in the labor force (1). As evidenced by the large proportion (67%) of women who work during their first pregnancy (2), most workers trust that the benefits of their employment outweigh any possible reproductive risks. Work does confer potential reproductive advantages. At a fundamental level, access to basic resources, such as adequate nutrition and health care, are dependent on income from work in most countries. In the United States, employment-linked health insurance, when available, largely funds the cost of prenatal, perinatal, and neonatal care. A minority of companies also provide coverage to deflect the cost of assisted reproductive techniques. Workplace programs that promote healthy lifestyles, when available, also directly and indirectly promote reproductive health. Some jobs, however, also engender defined and yet-to-be defined reproductive health risks that may or may not be fully comprehended by the worker or the employer. In such settings, faulty assumptions about risks and benefits of employment may ensue, with a resultant underestimation of the need to mitigate reproductive and other health risks. Physicians and nurses who serve workers are in a unique position to identify and help minimize many such risks and influence positive outcomes for workers and their children through education, surveillance, research, and advocacy. Accomplishment of this goal requires a proactive approach based on knowledge assimilated by communication with workers, clinical observations, other health and safety disciplines, the research literature, and policy making by advisory, regulatory, and legal agencies.

Adverse reproductive outcomes exact enormous emotional, health, and economic tolls on affected individuals and families, and have indirect costs for employers and society as well. Chances that an individual will experience some form of reproductive health or birth impairment are high. Approximately 10% of

[1] The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

couples report periods of infertility, though rates vary regionally (3), and about 5% are sterile (4). Couples may also experience very early and undetected fetal loss as infertility, with only an estimated 15% to 20% of failed conceptions being clinically recognized as miscarriages (5). Fetal losses after 20 weeks gestation, that is, stillbirths (6.4 per 1,000 births plus fetal deaths in 2002), and infant deaths (0.7% in 2003) added to the toll of recognized pregnancy losses based on currently released U.S. National Center for Health Statistics (NCHS) reports (6). Preterm deliveries (12.5% in 2004) and low birth weights (8.1% in 2004) were relatively common according to NCHS. Major malformations have been estimated to manifest in 3% of live births. A growing body of research suggests that predisposition to certain diseases of adulthood may originate in utero, the implication being that additional complications of pregnancy may manifest later during adulthood.

The primary cause of a reproductive failure is often unknown. Disruption in the intricate physiochemical balance within and between the paternal, maternal, and fetal systems could result in a broad range of adverse effects. Definitions of reproductive and developmental toxicity are often used interchangeably, but incorrectly. Reproductive toxicity has been defined as "the occurrence of adverse effects on the reproductive system that may result from exposure to environmental agents" and "may be expressed as alterations to the reproductive organs and/or the related endocrine system" (7). Developmental toxicity has been defined as "the occurrence of adverse effects on the developing organism that may result from exposure before conception (either parent), during prenatal development, or post-natal to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism" and "can include fetal death, structural abnormalities or birth defects, and functional deficiencies or altered growth" (7).

Reproductive and developmental toxicities of occupational and environmental exposures are potentially mediated by the complex interplay of toxicant activity, dosage, biologically effective dosage, and latency as well as by individual differences in maternal, paternal, and fetal metabolism, excretion, and storage. During the reproductive years, timing and dose of exposure relative to stage of ovulation, spermatogenesis, or pregnancy may influence the outcome(s). Further, potential vulnerability to toxicant effects varies throughout the life cycle, with some altering the maturation or future reproductive capacity during fetal or childhood development, and others acting on reproductive health or capacity during the reproductive years or beyond. For example, lead exposure has been implicated in delayed puberty among girls, sperm alterations among men, and congenital anomalies among children of exposed pregnant women (8,9).

Identifying and interpreting risks requires consideration of the multiple factors. Thus, the primary purpose of this chapter is to outline reproductive health problems, together with some approaches for conducting and interpreting human studies of effects of occupational and environmental exposures on these problems, using current and historical research examples to convey the scope of study methods and factors that may affect study findings.

ASSESSING THE FECUNDITY OF A COUPLE

The terminology of fertility can be confusing, and couples whose true probability of conception ranges from nearly normal to zero may be described as infertile in different contexts. The World Health Organization (WHO) defines infertility as failure to conceive after at least 1 year of unprotected coitus. Definitions of infertility used in epidemiologic studies may reflect a window for observed conceptions as short as 6 months or as long as 2 years. Variation in fertility statistics from different studies may also reflect differences regarding whether or not couples not attempting to conceive were included. Other study design elements, such as those that affect participant recall, may also affect estimates of infertility. For example, an overall age-adjusted prevalence of infertility of 20.6% was observed for couples who had not conceived after 2 years of unprotected intercourse using a life calendar approach. When the same couples were asked specific questions about their awareness of dates when they were unable to conceive after trying for 2 years, the overall rate dropped to 12.5% (10).

Fertility statistics are based on the ability to deliver a viable child, whereas fecundity addresses the physiologic capacity of individuals or couples to conceive. A couple is considered subfecund if the woman has difficulty becoming pregnant or sustaining a pregnancy over a specified period. Five main study approaches have been used to assess subfecundity. The first approach asks specific questions to determine whether the respondent has identified a period of time during which the couple was trying to conceive. Dates are obtained for the total period(s) when the couple was trying. The rate and length of time, in days, weeks, or months, when the couple was subfecund are compared for exposed and unexposed. Often a minimum of a full year of unprotected intercourse is the criterion. This interval encompasses about five sperm cycles, however, and may be problematic for exposures that are acute or intermittent (11).

A second approach used to assess subfecundity is outlined in a study of workers exposed to ethylene dibromide (EDB). This study compared the observed number of births for exposed person-years with an expected number estimated from birth rates specific to the mother's

age, parity, race, and year of birth, and examined the fertility experience, comparing exposure intervals (12,13). The disadvantage of this approach is that the observed and comparison groups may differ with regard to important covariates. For example, when national statistics are used as expected rates, information such as contraceptive history and infertility may not be considered, rates may be missing for some ages, cohorts, or parities, and marital status may not be comparable. Standardized fertility ratios consider only live births so that other important reproductive events are not included.

Methods to determine the number of contraceptive-free cycles required for a couple to conceive after complete termination of birth control offer a third approach to analyze subfecundity (14). These time-to-pregnancy (TTP) or time-to-delivery approaches incorporate a larger scope of reproductive experience, encompassing preconception and postconception events. Such studies can examine the effects of suspected toxicants on either the male or female partner, or on both partners, when applicable. For instance, significantly prolonged TTP has been associated with men's and women's workplace exposures to various solvents in some (15–17), but not other groups. TTP studies are generally conducted either prospectively or retrospectively. The prospective approach assesses TTP forward in time by following partners either from the time they start attempting conception and cease contraceptive use or without regard to their pregnancy intentions. The retrospective approach assesses TTP backwards in time, collecting data based on the recollections of partners who had a recognized pregnancy. Advantages and disadvantages of each approach have been recently reviewed (18). Prospective TTP studies can provide accurate information on sterility, spontaneous abortion, ectopic pregnancy, stillbirths, and completed pregnancies. Data are collected that may include information on menstrual cycles, contraception, and frequency of sexual intercourse. Analysis of such data may include adjustment for covariates such as cycle length, abstinence, and sporadic use of birth control. A retrospective TTP approach is relatively less expensive than a prospective approach but may entail increased potential for biases related to recruitment, recall, behavior (i.e., adoption of perceived fertility-promoting behaviors among those with prolonged TTP), and exposure trends (i.e., more opportunity for and duration of exposure with prolonged TTP), and so is most appropriate for exploratory and surveillance studies (18).

A fourth approach is the detailed prospective TTP study, involving collecting additional daily reported and biomarker data. This approach yields superior information on early pregnancy loss and permits more adequate adjustment for timing of intercourse. The detailed approach is expensive and more time-consuming, involving collection of data on menses, sexual activity, birth control, toxicant exposure, and biomarkers of exposure, endocrine status, ovulation, and pregnancy (18). Participation bias is a concern in such studies with so many requirements of participants; demographic information as well as feedback regarding reasons for those not participating is valuable.

A fifth "current duration" approach in which TTP is estimated from the unprotected sexual intercourse durations among couples currently having intercourse without contraception offers the advantage of a well-defined target population for establishing rates, with less potential for selection bias (19). This approach may be augmented by follow-up collection of pregnancy occurrences alone or additional detailed prospective data (18).

The choice of whether to conduct a TTP study or a standardized fertility analysis depends on both resources and the availability of a referent group. If a referent population is unavailable, the standardized fertility analysis is used. If a referent group is available and if considerable details are known on potential confounders, the TTP approach may be preferred.

The feasibility of examining trends in fertility over time via TTP (excluding unintended pregnancies) and fertility rate studies was tested by Sallmén et al. (20). Such trends are of interest related to current speculation regarding observed declines in sperm quality in recent decades that have been reported in some, but not all, regions (21–23). Sallmén et al. concluded, given biases resulting from changes in contraceptive use and availability over time and ascertainment of induced abortions, that detection of true biologic changes in fertility over recent decades is not highly feasible.

ASSESSING MATERNAL EXPOSURES AND REPRODUCTIVE OUTCOMES

Studies of the reproductive effects of toxicant exposure on female worker populations are unique because two individuals may be at risk—the woman and, if she is pregnant, her developing offspring. Reproductive health outcomes of concern with regard to maternal toxicant exposures may include subfecundity, menstrual disorders, endocrine disruption, illness during pregnancy, breast milk alteration, early onset of menopause, and suppressed libido. Adverse fetal outcomes include preterm delivery, fetal loss, perinatal death, low birth weight (LBW), altered sex ratio, metabolic or physiologic disorders, congenital malformations, childhood malignancies, infant or childhood illness, chromosome aberrations, and developmental disabilities. A number of reviews have been published on occupational exposures associated with adverse pregnancy outcomes (9,24,25). The following section discusses the potential effects of toxic exposure on pregnancy outcomes and menstrual cycle variability and the epidemiologic issues associated with investigating these outcomes.

Adverse Pregnancy Outcomes

Exposure of the conceptus to a toxicant can result in different effects depending on the phase of embryofetal development—early or late embryogenesis—or the fetal period of development in which exposure occurs. Transport time of a fertilized ovum before implantation is between 2 and 6 days. During this early stage, the embryo may be exposed to chemical compounds that penetrate into the uterine fluids. Insult during this period is seldom recognized, as zygote loss that occurs prior to implantation is unlikely to affect menses. It has been traditionally assumed that pre-implantation conceptuses are either killed by teratogenic insult at this early stage or survive without adverse sequelae, as cells are pluripotent and have not initiated differentiation. This assumption is supported by evidence from studies of radiation and chemotherapy exposure. Not withstanding, there is evidence of significantly increased levels of a benzo[a]pyrene derivative bound to DNA (DNA adducts) in human pre-implantation conceptuses of smoking compared to nonsmoking couples (26), and also animal studies also indicate that pre-implantation environmental conditions affect prenatal and postnatal development. Effects of environmental exposures on nonarrested human pre-implantation conceptuses are difficult to directly study without compromising their viability, and thus effects are speculative at the current time.

The period of late embryogenesis is characterized by differentiation, mobilization, and organization of cells into tissue and organ rudiments. It is clear that the developing human fetus is exposed to many toxicants in utero. The toxicokinetics and biologically effective dosages of these chemicals in human fetuses are less clear. A recent study examined chemicals in the cord blood of 10 live U.S. newborns selected randomly from the Red Cross's national cord blood collection program. Cord blood analyses detected 180 potential human or animal carcinogens, 217 with neurologic effects and 208 possible teratogens in animals (26a). That these newborns were selected randomly, and not based on the manifestation of adverse birth outcomes, suggests much work remains to determine if exposure levels encountered in utero place the embryo or fetus at increased risk. Wilson's (27) classic work outlined many of the possible mechanisms in structural malformations: mutation, chromosome damage, mitotic interference, altered nucleic acid integrity, lack of precursors, altered energy sources, enzyme inhibition, and alteration in membranes. More recently, aberrant epigenetic regulation of gene function has been identified as an underlying mechanism for various infant developmental defects and syndromes (28). The term epigenetic refers to "heritable changes in gene expression that occur without a change in DNA sequence"(27a). Factors that mediate susceptibility to defects include embryonic stage at the time of exposure, exposure route, level of exposure relative to the threshold dose for toxicant damage, mechanism of toxicant action, maternal and fetal toxicant metabolism and kinetics, placental receptors, transport, and bioconversion, and genotype (29). Extrinsic factors such as nutritional deficiencies or the additive, synergistic, or antagonistic effects associated with multiple exposures may further affect response. Untoward responses during embryogenesis can culminate in spontaneous abortion, gross structural defects, fetal loss, growth retardation, or developmental abnormalities.

The fetal period extends from embryogenesis to birth and is characterized developmentally by growth, histogenesis, and functional maturation. Toxicity may be manifested by a reduction in cell size and number. The brain remains sensitive to injury: Myelination is incomplete until after birth. Growth retardation, functional defects, disruption in the pregnancy, behavioral effects, transplacental carcinogenesis, or death may result from toxicity during the fetal period. The following discussion reviews the biologic, sociologic, and epidemiologic issues concerning the process of evaluating occupational exposures and fetal loss, congenital anomalies, preterm delivery, and LBW. Definitions, estimated incidence rates, and risk factors associated with specifics outcome are described below.

Fetal Loss

The developmental stages of the zygote, defined in days from the last menstrual period (LMP) and days from ovulation (DOV), proceed from the blastocyst stage at days 15 to 20 (1 to 6 DOV), with implantation occurring on day 20 or 21 (6 or 7 DOV), to the embryonic period from days 21 to 62 (7 to 48 DOV). The fetal period extends from day 63 (49+ DOV) until the designated period of viability, which ranges in reports from 140 to 195 days. Estimates of the probability of pregnancy termination at any one of these stages depend on both the definition of fetal loss and the methods used to measure the event. The total proportion of pregnancies that are lost has been estimated at 70%, with 30% lost prior to implantation, 30% after implantation when only detectable biochemically, and 10% identified as clinical miscarriages (5). In a landmark study using human chorionic gonadotrophin (hCG) methods (30), the incidence of postimplantation subclinical loss of fertilized ova was 22%, and 9% of losses were recognized. Subsequently, reported incidences of subclinical and clinical pregnancy losses varied somewhat across locales and timeframes, according to different definitional gestational cutoffs, and hCG assays used. While subclinical pregnancy losses are often described as early fetal losses in the research literature, "early fetal loss" generally refers only to clinically recognized losses, that is, spontaneous abortions, in vital statistics reports.

Definitions applied to distinguish earlier fetal losses (i.e., spontaneous abortion or miscarriages) from later fetal losses (i.e., stillbirths) vary widely within and between nations, both with regard to gestational age, fetal weight, and, in some instances, length criteria. These differing definitions reflect, in part, regional differences in survival outcomes for very premature infants. International definitional differences may also affect classification of early gestation deaths as "fetal" versus "infant" deaths. Varying rates of recognized fetal loss reported based on prospective versus retrospective or cross-sectional study designs may be attributable to differences in underlying definitions, misreporting of induced abortions as spontaneous, or misclassification of a delayed or heavy menses as fetal loss. The WHO defines early neonatal death as the death of an infant aged 7 days or younger and late neonatal death as demise between 7 and 29 days. For studies conducted in developing countries, it may be important to distinguish between prepartum and intrapartum deaths. In examining late fetal losses, it may be appropriate to include early neonatal deaths (excluding birth trauma deaths) as the causes may be similar.

Occupational studies have often used records or questionnaire data to identify spontaneous abortions. Recorded data sources include vital statistics and hospital, private practitioner, and outpatient clinic records. Questionnaire data are collected with mailed instruments or in personal or telephone interviews. Use of record systems identifies only a subset of all fetal losses, principally those that occur after the start of prenatal care, typically after two or three missed periods. By interviewing women to obtain reproductive histories, more complete documentation of all recognized losses is possible. Questions that are usually included in reproductive histories include all pregnancy outcomes, prenatal care, family history of adverse pregnancy outcomes, marital history, nutritional status, prepregnancy weight, height, weight gain, use of cigarettes or alcohol, prescription and nonprescription drugs, health status of the mother during and prior to a pregnancy, and exposures at home and in the workplace. Relevant exposures may include biologic, chemical, and physical agents and conditions (31) and psychological stressors. Information concerning exposure dates and intensity of exposure to specific agents within these broad categories is desirable to minimize misclassification; however, the limitations of retrospective recall must also be weighed during questionnaire development. Detailed, quantitative exposure histories are often more readily reconstructed in industry-based studies than in community-based studies, particularly when industrial hygiene monitoring or biomonitoring data are available for the periods of interest.

The validity of self-reported pregnancy histories as reported in six studies in a 1989 review was verified in hospital or physician records at a rate between 57.5% and 91.8% (median 86.2%) (32). Not unexpectedly, Wilcox and colleagues found only 54% of fetal losses before 7 weeks gestation were confirmed in records, but by 9 to 12 weeks gestation, 82% were recorded, and at 13 weeks gestation, 93% were reported (33). The interval between the fetal loss and time of interview may be associated with memory errors and a reduction in validity. In that study, if the interview occurred within 10 years of the event, recall of spontaneous abortions was 82% complete. These results suggest that errors of recall of early fetal loss and spontaneous abortion before 13 weeks of gestation are of sufficient magnitude to mask subtle effects or, if systematic, introduce misclassification bias. Recall of later spontaneous abortions and birth weights appears more robust. The extent to which increased access in recent decades to home ovulation and pregnancy testing and assisted reproduction may affect maternal and paternal recall of pregnancy-related outcomes, particularly early pregnancy loss, remains to be determined. Recall of birth weights appears robust, as a high correlation ($r = 0.98$) between medical records and maternal interviews has been reported for birth weight (34).

Multiple potential physical, genetic, social, psychological (stress, for example), and environmental factors have been potentially associated with spontaneous abortion and recurrent pregnancy loss. Table 12.1 lists some factors that have been the subject of human studies. When designing studies of birth outcomes, such as pregnancy loss, the strength of current evidence regarding such factors informs the identification of relevant factors for matching or exclusion criteria, potential confounders or effect modifiers, and the potential usefulness of the data for understanding outliers. As a research consumer, the weight and quality of current evidence regarding such factors is important to consider when assessing methods and results of studies. The link between fetal loss and some factors is fairly well-established. Infections associated with fetal loss include syphilis, rubella, genital *Mycoplasma* infections, herpes simplex, uterine infections, bacterial vaginosis, general hyperpyrexia, and others. One of the most important risk factors for clinically recognized spontaneous abortion is a history of fetal loss. Higher gravidity is associated with increased risk, but this may not be independent of a history of spontaneous abortion. Interpretations of gravidity as a risk factor conflict because of its association with maternal age, reproductive history, and heterogeneity of women at different gravidity ranks. Rates of spontaneous abortion are higher for women younger than 16 and older than 36 years. After adjusting for gravidity and a history of pregnancy loss, women older than 40 years had twice the risk of fetal loss of women 20 years of age (35). The risk increase for older women occurs in tandem with an increase in chromosome anomalies, particularly trisomy (36).

Table 12.1

Some Variables Presented in the Human Research Literature of Potential Interest for Studies of Selected Birth Outcomes[a]

Variables	Fetal Death	Prematurity	Low or Lowered Birth Weight[b]
Environmental and Occupational Variables[c]			
Socioeconomic/educational status (low SES?)	✓	✓	✓ (s, i)
Marital status (single?)		✓	✓ (l)
Prenatal care (poor?)		✓	✓ (l)
Caffeine intake (high?)	✓	✓	✓ (l, s)
Maternal tobacco smoking history	✓	✓	✓ (l, s, i)
Environmental tobacco smoke/paternal smoking history	✓	✓	✓ (l, s, i)
Prescribed and	✓		
recreational drugs	✓	✓	✓ (l)
Maternal alcohol use	✓	✓	✓ (l, s)
Paternal alcohol use	✓		
Malnutrition		✓	✓ (l)
Physical work (standing, lifting, long hours, shift work)	✓	✓	✓ (l)
Maternal injury	✓		
Psychological stress	✓ (e.g., work stress, recent life events)	✓ (e.g., work stress, distress)	✓ (l) (e.g., distress)
Abuse	✓	✓	
Maternal organic solvent exposure	✓ (e.g., glycol ethers, benzene, toluene)		✓ (l) (e.g., certain aromatic hydrocarbons)
Paternal organic solvent exposure	✓ (e.g., ethylene oxide, toluene)	✓ (e.g., printing solvents)	✓ (l) (e.g., benzene)
Maternal heavy metal exposure	✓ (e.g., lead)	✓ (e.g., lead)	✓ (l) (e.g., lead)
Paternal heavy metal exposure	✓ (e.g., mercury)		✓ (l) (e.g., lead)
Maternal pesticide exposure	✓ (e.g., DDT)	✓ (e.g., DDT; 2,4-D)	✓ (l) (e.g., pyrethroids, dioxin)
Paternal pesticide exposure	✓ (e.g., DBCP, certain fungicides)	✓	
Maternal antineoplastic administration	✓		
Maternal electronics exposure	✓ (e.g., semiconductor workers)		
Maternal electromagnetic radiation exposure	✓		
Maternal ionizing radiation exposure	✓		✓ (l)
Paternal ionizing radiation exposure	✓		
Maternal petrochemical exposure	✓		
Maternal anesthetic gas exposure	✓ (e.g., nitrous oxide)		
Paternal anesthetic gas exposure	✓		
Air pollution		✓	✓ (l, i)
Altitude			✓ (l)
Medical and Sociodemographic Variables			
Maternal age (advanced and teenage pregnancy)	✓	✓	✓ (l, s)
Advanced paternal age	✓		
Low maternal weight, BMI, or poor weight gain		✓	✓ (l, s)

Low maternal height		✓	✓ (s)
Maternal obesity	✓	✓	✓ (s)
Short interval between pregnancies	✓	✓	
Parity	✓	✓	✓ (l, s)
Birth order		✓	✓ (l, s)
Race	✓	✓	✓ (l)
Sex of conceptus	✓	✓	
Timing of conception vs. ovulation	✓		
History of infertility	✓	✓	✓ (l)
History of fetal death	✓	✓	✓ (s)
History of induced abortion	✓	✓	
History of premature delivery		✓	✓ (l, s)
History of LBW or SGA births		✓	✓ (l)
Family history			
Assisted reproduction		✓	✓ (l)
Prematurity	✓		✓ (l)
Maternal hormone imbalance	✓		
Maternal diabetes	✓	✓	✓ (l,i) (iatrogenic)
Polycystic ovarian syndrome	✓		
Immunologic factors	✓	✓	✓ (l)
Other thrombophilic defects	✓		
Factor V Leiden mutationhyperhomocystinemia	✓		
Maternal thyroid disease	✓	✓	
Uterine or cervical defects	✓	✓	✓ (l)
Maternal genital tract infections	✓ (e.g. bacterial vaginosis)	✓ (e.g., bacterial vaginosis)	✓ (l, s) (e.g., chlamydia, *trichomonas*)
Other maternal infections	✓ (e.g., HIV, malaria)	✓ (e.g., urinary tract, periodontal)	✓ (l, i) (e.g., malaria, periodontal)
Maternal hypertension/pre-eclampsia	✓	✓ (e.g., iatrogenic delivery)	✓ (l, s) (e.g., iatrogenic delivery)
Placental or cord alterations	✓ (e.g., cord prolapse, placenta abruptio)	✓ (e.g., placenta previa, abruptio → iatrogenic delivery)	✓ (l, s) (e.g., placenta previa, abruptio → iatrogenic delivery)
Other maternal or fetal compromise → iatrogenic delivery		✓	
Other maternal systemic diseases	✓ (e.g., chronic renal disease, celiac disease	✓ (e.g., chronic renal disease)	✓ (l,s,i) (e.g., chronic renal disease, hypexemia states)
Anemia		✓	✓ (l, i)
Multiples (spontaneous or in vitro conceptions)	✓	✓	✓ (l, s)
Chromosome anomalies/malformations	✓	✓	✓ (l, s)
Genetic predisposition	✓ (e.g., PKU, G6PD)	✓ (e.g., family history of prematurity)	✓ (l, s) (e.g., heritability in twin studies)

[a]Variables may be of interest, for example, as descriptors, exclusions, covariates, confounders, matching criteria, or for outlier or results interpretation in some studies.
[b]Variables of interest based on findings of: [l], low(ered) birth weight; [s], small for gestational age; or [i], intrauterine growth restriction.
[c]Relevant information may include specific exposure(s), dose, duration, latency, and timing in relationship to periconception and gestation.
Inclusion of an exposure on this variable list does not necessarily imply an association with birth outcomes is well-established.
DDT, dichlorodiphenyltrichloroethane; DBCP, 1,2-dibromo-3-chloropropane; BMI, body mass index; LBW, low birth weight; SGA, small for gestational age; PKU, phenylketonuria; G6PD, glucose-6-phosphate dehydrogenase deficiency.

Consensus is less clear for some of the other factors identified in the tables. For example, authors of a recent review of 15 studies of caffeine intake during pregnancy and spontaneous abortion concluded that a causal link between caffeine and spontaneous abortion was equivocal (37). While mostly positive associations were reported, pregnancy-specific analysis issues, such as accounting for the fetal karyotype, the timing of fetal demise, and the possibility that caffeine's effects depend on gestational age at exposure as well as more general issues of bias, were sources of ambiguity. Lawson and Lemasters (38) recommended future studies of coffee and pregnancy loss should be conducted longitudinally, with repeated measures and consideration of pregnancy-induced coffee aversion, based on their findings linking coffee consumption and aversion to hormonal fluctuations during pregnancy.

Employment status may be a risk factor regardless of a physical or chemical hazard and may act as a confounder in assessment of occupational exposure and spontaneous abortion. Women who stay in the workforce may be more likely to have had an adverse pregnancy history, or this group may be an inherently fitter subpopulation. In a report of 3,315 pregnancies, it was found that employed women had a significantly higher rate of spontaneous abortion (14.5%) than those unemployed (11.7%; risk ratio = 1.23; 95% confidence interval = 1.02 to 1.49) (39). Another study of 3,712 employed and 2,215 unemployed women indicated that working women had more favorable demographic and behavior characteristics, such as higher income and earlier prenatal care, but a less favorable reproductive history (40).

Congenital Anomalies

Historically, the terms *terata* and *congenital malformation* refer to structural defects present at birth that may be gross or microscopic, internal or external, hereditary or nonhereditary, single or multiple. *Congenital anomaly* is broadly defined and includes abnormal behavior, function, and chemistry with malformations as one type of anomaly. Malformations, which are generally attributed to intrinsic alterations in embryonic development or structure differentiation, may be distinguished from other anomalies attributed to intrauterine molding (deformations) or the destruction of normal structures (disruptions) (41). A major malformation can be defined as one that results in death, requires surgery or medical treatment, or constitutes a substantial physical or psychological handicap. Overall, the prevalence of major defects ranges between 1% and 7%, while the reported prevalence of minor defects varies widely, that is, between 2% and 36% (42,43). Chromosome defects generally produce multiple defects, whereas single-gene changes or exposure to environmental agents may cause either single defects or a syndrome.

Reviews of the potential causes, mechanisms, and types of malformations are available (44). The incidence of malformations depends on the status of the conceptus—live birth, abortus, or stillbirth. Chromosomal abnormalities have been documented in 50% to 70% of spontaneously aborted pregnancies. Miller and Poland (45) detected abnormalities in 88% (73 of 88) of spontaneously aborted conceptuses up to 28 days of gestation, and in 43% (223 of 498) of total spontaneously aborted conceptuses up to 20 weeks of gestation. In the early age group, multiple-system defects and severe growth disorganization were found; these anomalies became less frequent with each developmental stage. With the introduction of prenatal screening and increased rates of elective termination of anomalous fetuses, the surveillance of birth defects and associated risk factors is incomplete without adjustment for the frequency of induced abortions. This issue is particularly relevant for specific defects that are more frequently detected and severe and, consequently, more likely to be aborted. As fetal surgery to correct malformations in utero becomes more prevalent, it may also affect the observed incidence of certain malformations at birth. Birth defect incidence figures for live births also depend on the age at diagnosis and vary with the information source (birth certificates, hospital records, parental reports, and physician reports) definitions of defects, ascertainment method, and specialty of the examining clinician. Some congenital malformations go undetected at birth and only become evident months to years later.

Overall malformation rates are approximately 40% higher for boys than for girls (46). Much of the excess in malformation rates observed among boys may be directly or indirectly related to male gonad development with attending increased risk of errors, X- or Y-linked genes that influence development before and after gonadal development, the periconception endocrine milieu, and differential prenatal mortality. Male conceptuses reportedly outnumber female conceptuses by approximately 3:2 during the first 2 months of pregnancy (47), but at birth, the "secondary" male to female ratio is reduced to approximately 1.06:1. Although boys are at higher risk for most major malformations, girls have higher rates of cleft palate and neural tube defects (48). Relatively frequent anomalies in both sexes include oral clefts, clubfoot, neural tube defects, cardiac anomalies, polydactyly, syndactyly, limb deficiencies, congenital hydrocephalus, and trisomy 21 (Down's syndrome).

Birth defects remain the leading cause of infant death in the United States, with 60% of these deaths attributable to anomalies of the cardiovascular, respiratory, and nervous systems (49). Brent estimates that birth anomalies detected within the first year of life are caused by genetic factors (15% to 25%), including

sex-linked and autosomal genetic conditions, chromosomal abnormalities, and new mutations, and environmental factors (10%), including maternal conditions (4%), infectious agents (3%), mechanical deformations (1% to 2%), and chemicals (<1%) (29). The cause of the remaining 65% to 75% of these defects is categorized as unknown. Polygenic, gene-environment interactions, spontaneous development errors, or synergistic activity of teratogens have been posited as mechanisms. Finnell et al. (41) have reviewed current insights into the molecular mechanisms by which environmental agents act to induce birth defects.

Several recent reviews have presented studies of birth defects across maternal and paternal occupations and workplace exposures (50–52). Shi and Chia (51,52) summarized evidence linking birth defects and occupation for subsets of male and female workers in broad occupational groups, including healthcare workers, laboratory and solvent-exposed workers, workers with electromagnetic radiation exposure, certain service sector workers, leather and textile dye workers, printers, fire fighters, agriculture workers, and chemical workers. Many of these links were considered inconclusive, in part, because of methodologic issues and the small number of human studies of each specific exposure. Some links are currently disputed.

The past several decades have witnessed controversy and an increased research focus on possible effects on offspring of periconceptional and fetal exposure to chemicals that have endocrine activity, such as many pesticides, phthalates, and bisphenol A. Interest has been generated by the inconsistent body of evidence from human studies suggesting temporal changes in the incidence of several interrelated, endocrine-linked outcomes, such as hypospadias, cryptorchidism, testicular cancer, and regional declines in sperm count and proportions of male births. A small number of studies have examined relationships between maternal or paternal exposures to agriculture or pesticides and cryptorchidism or hypospadias, with both positive (53–55) and negative (56,57) findings; a number of other studies have identified positive associations with other anomalies (58). Significant inverse correlations between urinary phthalate metabolite levels and anogenital distance, a marker of antiandrogen exposure in animal studies, were recently described among boy infants without malformations (59). Various solvents encountered in occupational and environmental settings by fathers or mothers have been linked to anomalies such as neural tube, neural crest, congenital heart, and other defects in several, but not all, studies (50,60–62).

Several other environmentally mediated factors have been strongly associated with congenital anomalies in offspring. Such factors include exposure to teratogenic drugs and infections, maternal dietary folate deficiency linked to neural tube defects, and high ethanol consumption associated with fetal alcohol syndrome. Prenatal exposure to high doses of ionizing radiation has been associated with central nervous system (CNS) and growth defects, and low doses of lead have been associated with neurobehavioral and cognitive deficits (63,64). Methylmercury was historically one of the first recognized reproductive environmental toxicants, as evidenced by morphologic, CNS, and neurobehavioral abnormality outcomes resulting from maternal consumption of contaminated food in Japan and Iraq (65,66). In Japan, the cluster of cases was linked to consumption of fish and shellfish contaminated with mercury derived from the effluent of a chemical factory. In the United States, newborns whose mothers consumed polychlorinated biphenyls (PCBs) by eating fish, as evidenced by increased high maternal serum and breast milk PCB levels, had significantly lower full-scale and verbal IQs than nonexposed children at 11 years of age (67).

An area under current study is how certain genes may mediate susceptibility to congenital effects of prenatal exposures on offspring. Examples include studies of birth defects and their relationships to ethanol exposure and smoking. One positive association is that certain maternal and fetal polymorphisms of alleles in the alcohol dehydrogenase enzyme family (ADHB1's) appear protective against fetal alcohol syndrome in studies of mixed South African ancestry and African American populations (68). Evidence from a metaanalysis of 24 studies linked oral clefts to smoking (69) and some, but not all, studies suggest transforming growth factor-α polymorphisms may modify this risk to smokers' offspring (70). One study found a family history-smoking interaction for occurrences of clubfoot (71). The odds of clubfoot among children with both smoking mothers and positive family histories were 15 times higher than among children of smoking mothers only and three times higher than among children with family history of clubfoot only. Such findings illustrate the potential of gene-environment studies to detect effects of exposures on subgroups of children that may remain undetected when genotype and family history are not examined.

The relatively low prevalence of congenital anomalies present at birth or within the first year of life presents challenges for studying potential contributions of occupational and less common environmental exposures. The biggest challenge is having a sufficient sample size to measure individual defects. Another challenge in studying malformations is deciding how to group anomalies for analysis. Often, all malformations are combined or the combination is based on major and minor categories. The advantage of grouping them all together is that the total number of cases is increased, and, therefore, the statistical power is increased. If, however, the exposure effect is specific to a particular type of malformation (e.g., CNS), such grouping could

mask an effect. Alternatively, malformations may be grouped by organ system. Though this method may be an improvement, certain defects may dominate the class, such as varus deformities of the feet in the musculoskeletal system. Given a sufficiently large sample, the optimal approach is to divide the defects into pathogenically homogeneous groups. Consideration should be given as well to the exclusion or inclusion from these groups of certain anomalies, such as those that are likely caused by chromosome defects, autosomal dominant conditions, or malposition in utero.

Sex Ratios of Offspring

Altered ratios of boys to girls at birth, that is, secondary sex ratios, have also been examined as endpoints in studies of environmental and occupational exposures. The premise is that such exposures may affect the "primary" sex ratio at conception or selectively increase the postconception fetal loss rate as a result of lethal anomalies or other conditions for one gender versus the other. Theories regarding the cause of altered secondary sex ratios have been proposed, including variation in periconception and intrauterine hormonal levels, intercourse timing relative to ovulation/oocyte maturity, sexual behavior, adaptive responses to environmental stressors, and actions of toxicants. Reported sex ratios are calculated by different formulas in the literature and so may require conversion to be directly compared.

Lowered secondary sex ratios (males/males + females) have been observed among offspring of male carbon setters and pesticide workers. The sex ratio of children born to carbon setters fathers (0.381, $n = 139$) was significantly lower than the ratio born to the comparison group of aluminum worker fathers (0.512, $n = 2{,}787$) (72). In one study of dioxin-exposed pesticide production workers, the sex ratio of children born to production worker fathers (0.378, $n = 188$) was significantly lower than the ratio born to production worker mothers (0.513, $n = 39$) and to the exposed community comparison group (0.512, $n = 66{,}695$) (73). In contrast, Schnorr et al. (74) did not find differences in sex ratios of the offspring of highly TCDD (2,3,7,8-tetra chlorodibenzo-p-dioxin) exposed production worker fathers ($n = 281$) compared with neighborhood controls ($n = 260$). Another investigation found a significantly lower sex ratio for births to pesticide applicator fathers who applied fungicides (0.445, $n = 508$) than for births to applicator fathers who only applied herbicides (0.529, $n = 342$) (75). Paternal exposure to dibromochloropropane (DBCP) during its production resulted in a significant decline in the prevalence of male births from 52% to 35%, respectively, for births conceived before and after exposure (76). A lowered secondary sex ratio (0.458, $n = 286$) was also shown among children of men exposed to PCB before age 20 years during the above mentioned Yucheng oil disaster in comparison with children of men exposed after age 20 (0.541, $n = 183$) and nonexposed age and neighborhood-matched controls (0.542, $n = 705$, odds ratio 0.65, 95% confidence interval 0.45 to 0.93) (77).

Internationally, regional trends of declining secondary sex ratios have also been documented. Socioeconomic conditions and stressors, such as those associated with altered secondary sex ratios during war and famine, are generally posited to explain the temporal and regional variation in secondary sex ratios. Consistent patterns of effects of environmental pollution on secondary sex ratios at the population level are absent to date.

Low Birth Weight and Preterm Delivery

WHO recommends the definition of *preterm* as delivery before 37 completed weeks of gestation, less than 259 completed days from the first day of the LMP. LBW was defined as less than 2,500 g, and very LBW as less than 1,500 g. Significant fetal weight gain does not begin until the second trimester. The conceptus weighs approximately 1 g at 8 weeks, 141 g at 12 weeks, and 1.1 kg at 28 weeks. An additional 1.1 kg is gained every 6 weeks until term. The normal newborn weighs approximately 3,200 g at term. Gestational age is generally measured from the onset of the LMP to the date of delivery. Since ovulation occurs approximately 2 weeks after onset of the LMP, errors may occur in estimation of gestational age by 1 to 4 weeks, depending on the variability of the menstrual cycle. Accuracy of gestational age by this method depends on the woman's recall of the LMP or the physician's calculation of the expected delivery date. Ultrasound pregnancy dating can improve accuracy. The accuracy of vital statistics records depends on both pregnancy dating and accurate recording in the hospital records and on birth certificates. Thus, the opportunity for error is high.

Other analysis issues must also be considered to improve the interpretability of prematurity and LBW data. Infants defined as LBW may be so because they were premature, experienced restricted intrauterine growth, are inherently small, or a combination of these factors. In a study of 52,621 births, Savitz and colleagues reported that only 50.2% of preterm infants were LBW and 69.2% of LBW infants were preterm. Only infants at the lower extremes of both birth weight and gestation almost always met both LBW and preterm criteria (78). The authors, therefore, advocated using the separate designations of prematurity (using several gestational cutpoints) and small for gestational age as birth outcome measures, urged caution in comparing results of studies using overlapping measures, and recommended standardization of outcome measures in future studies. Typically, small for gestational age status is assigned when an infant's birth weight is statistically low compared with the

birth weights of other infants of the same gestational age (i.e., less than the lower limit of the confidence interval). A related concept, intrauterine growth restriction, has been defined as "a process of whatever etiology that can limit the potential for intra-uterine growth of the fetus, resulting in low birth weight" (79). It may also be important to distinguish between symmetric and asymmetric growth retardation. Asymmetric growth retardation (i.e., weight is affected more than skeletal structure) is associated principally with a risk factor operating late in pregnancy; symmetric growth retardation may more likely be associated with a cause operating over the entire length of gestation, such as malnourishment. Differentiating iatrogenic preterm births performed to optimize the health of growth restricted or multiple infants from those due to infections, bleeding, premature labor, or other maternal complications, has prognostic significance.

Among the many factors linked to infant survival, physical underdevelopment associated with early delivery, LBW, or both, presents the greatest risk in the United States. In developed countries, if respiratory distress is included as one of the complications of preterm delivery, preterm labor and LBW are directly or indirectly responsible for more neonatal deaths, mental retardation, and neurologic and ophthalmic disorders than any other single cause. Between 1990 to 2004, U.S. rates of preterm and LBW births increased 1.9% and 1.1%, respectively (80,81). Rates of preterm and very preterm (i.e., less than 32 completed weeks of gestation) births have modestly declined among non-Hispanic, African American mothers during this period, while they have increased among other groups. In 2004, the percentages of preterm and very preterm births, respectively, were 17.8% and 4.04% for African Americans, 11.5% and 1.63% for whites, and 12.0% and 1.76% for Hispanics. Tandem racial differences in percentages of LBW and very LBW births were also noted, with 13.7% and 3.14% reported for African Americans, 7.2% and 1.20% for non-Hispanic whites, and 6.8% and 1.19% for Hispanics.

Although intrinsic factors, such as heredity, appear to contribute to differing risks of prematurity and LBW, nonintrinsic factors are also clearly important. One estimate attributed 40% of birth weight variation to heredity and 60% to environmental factors (79). The impact of these combined influences on the risk of premature delivery and LBW is also evidenced by the dramatic differences in estimated rates between developed and developing countries. Internationally, the estimated incidence of LBW in developed countries ranges from roughly 5% to 8%, and is approximately 19% in developing countries (82); preterm birth estimates range between 5% and 12% in developed countries and account for 25% of births in developing countries. Comparisons of international figures for prematurity and LBW must be considered tentative, however, as only half of newborns are weighed, and the gestational age is known for still fewer (83). The relative contribution of various risk factors also varies widely between more and less affluent regions of nations and the world. For example, many preterm births in the United States and Canada are iatrogenic deliveries (labor inductions or cesareans) of mildly preterm (34 to 36 week gestation) infants; this has been linked to reduced stillbirth and has occurred in an era of obstetrical and neonatal care advances with lowered mortality of mildly preterm infants (84). In contrast, infectious diseases, such as malaria, account for much of the risk in developing countries.

An important environmental exposure associated with LBW and preterm delivery is cigarette smoking. Smoking during pregnancy approximately doubles the risk of LBW and causes an overall weight deficit of 75 to 400 g (85,86). Several studies have demonstrated that the average biparietal diameters of the offspring of mothers who smoke are significantly smaller than those of nonsmokers (87). Statistically significant and nonsignificant trends linking passive environmental tobacco smoke exposure among nonsmoking mothers to reduced birth weights have been reported in a number of studies (85,88–90). Explanations for these reductions in fetal weight and growth vary, and multiple mechanisms may be involved. Fetal hypoxia, reduced umbilical/placental circulation, and toxic influences on the placenta have been proposed. Nicotine is a powerful vasoconstrictor. Nicotine and carbon monoxide are both transferred rapidly and preferentially across the placenta. Alterations in the uterine, umbilical, or placental circulatory structure or hemodynamics of smoking mothers have been reported. Carbon monoxide levels in cigarette smoke range from 20,000 to 60,000 parts per million; carbon monoxide has an approximately 200 times greater affinity for hemoglobin than oxygen (91). Thus, the oxygen-carrying capacity of maternal, and especially fetal, blood is reduced, diminishing the amount of oxygen available to fetal tissues. Considered together, these findings suggest a smoking-related reduction in the exchange of nutrients and gases in the developing fetus. Apoptosis may also play a mechanistic role, as significantly increased levels of apoptosis have also been reported in the placentas of smoking mothers with small-for-gestational-age infants, compared with placentas of nonsmoking mothers of normal-weight infants (92). The relationship between smoking and LBW is further strengthened, however, by findings that the weights of infants of mothers who smoke vary in expected directions when mothers change their smoking status during pregnancy (93) and by studies suggesting that maternal and infant genes involved in tobacco metabolism

may modify the risk of preterm and lower weight births to smoking women (94,95).

Probably the most widely used and researched exposure associated with fetal growth retardation (as well as congenital anomalies) is ethanol. A case-control study by Ulleland (96) was the first to demonstrate an association between maternal alcohol consumption and LBW. In a prospective study of 9,236 births, Kaminski et al. (97) noted that many of the characteristics of heavy drinkers (older mother, unmarried, high-parity, low socioeconomic level, smokers, and early pregnancy bleeding) were also risk factors for adverse pregnancy outcomes. After adjusting separately for each of these risk factors, however, Kaminski found that prenatal consumption of more than 1.6 ounces of alcohol per day was still associated with an increased rate of stillbirth, LBW, and intrauterine growth retardation. For studies of other occupational or environmental exposures, it is important to ascertain good smoking and drinking histories and to gather these in a manner that avoids provoking guilt.

Ambient environmental and occupational gestational exposure to lead has been associated with early delivery. Andrews et al. (98) reviewed the literature on the link between lead exposure and pregnancy outcomes including premature rupture of membranes, prematurity, and LBW. The authors concluded that the evidence supported a relationship between prenatal lead exposure and risks of prematurity and LBW, but not premature rupture of membranes. They also elaborated on some of the constraints encountered when weighing the evidence, including differences between studies in exposure and dose characterization, pregnancy outcome categorization, failure to control for confounding, or over-controlling for questionable confounders, which were strongly related to exposure and only marginally related to disease risk.

In evaluating the possible effects of exposure on birth weight and gestational age, some problematic issues must be considered. Before the effects of exposure on LBW are evaluated, preterm delivery should be analyzed as a possible mediating outcome. The duration of a pregnancy is directly correlated with weight of the offspring. Further, duration of exposure can also be correlated with gestational length. Longer pregnancies afford more opportunity for exposure of workers. If enough women work late in pregnancy, the longest cumulative exposure may be associated with the oldest gestational ages and heaviest babies purely as an artifact (99). A number of procedures can be used to overcome this problem, including a variant of survival analyses handling time-dependent covariants. Preterm delivery and LBW can be defined as either dichotomous or continuous variables. The problem with defining birth weight as dichotomous is that valuable information—the specific weight—is lost.

ASSESSING MENSTRUAL CYCLE VARIABILITY AND FEMALE HORMONE ALTERATIONS

Research focused on the impact of occupational exposures on menses and the endocrine milieu that governs menstrual cycles and reproduction has been limited. Women compose about half of the work force, however, an observation that highlights the relevance of such studies. Toxic exposures can alter the pattern of menstruation by several means, including inhibition or damage to the follicles, effects on the CNS leading to endocrine alterations, damage to the hormone-secreting organs, or disruption of the hormone balance that regulates ovulation and the menstrual cycle. Blood measurements of pituitary gonadotropins and ovarian steroid hormones are traditionally measured for medical diagnoses. However, noninvasive measurements are more feasible for researchers and tolerable for participants in field studies, given the need for serial sampling—preferably daily sampling—over one or more menstrual cycles to adequately characterize female reproductive endocrine profiles. Kesner at al. (100) and others have developed and validated methods to identify menstrual cycle alterations using data from daily menstrual diaries and urinary endocrine analyses. Algorithms are applied to daily levels of urinary gonadotropin [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] and principle metabolites of the ovarian hormones progesterone (pregnanediol 3-glucuronide) and estradiol (estrone 3-glucuronide) to create variables describing endocrine concentrations and patterns of menstrual cycles. Baird et al. identified four urinary endocrine endpoints that distinguish conceptive versus non-conceptive ovulatory menstrual cycles by analyzing these algorithms applied to samples obtained during a TTP study (101).

At birth, infant girls' ovaries have between 3 and 4 million follicles each. By puberty the number is fewer than 400,000. During each ovarian cycle a number of follicles start to mature, but most fail. After menopause, few if any follicles are present in the ovaries. Animal studies have demonstrated that reproductive senescence can occur if xenobiotic agents block oogenesis in the fetus or destroy oocytes, causing premature ovarian failure. The estimated mean age at natural menopause is 50.5 years. The complex process of ovulation affords several potential targets for damage. Damage to the ovulatory process may be expressed in disorders of menstruation, which in turn may be a surrogate of other events such as a decrease in fertility potential or very early pregnancy loss.

Although the characteristics of a normal cycle vary between women, variations in individual women are slight. The average age of menarche is 12.5 years (range 9 to 16 years), the average duration is 2 to 7 days, and the interval between menses ranges from 23 to 35 days

(mean 28.1 days). Variation in the interval between menses for an individual should not exceed 5 days. During each menses the average blood loss is 30 to 100 mL. Menstrual abnormalities can be broadly divided into three categories: (a) cycle length or rhythm, (b) characteristics of bleeding patterns, and (c) the presence of pain.

The most dramatic disruption of cycle rhythm is complete absence of menses. The two types of amenorrhea are primary, the failure to menstruate by age 16 years, and secondary, cessation of menses for 3 months or longer before age 40. Polymenorrhea is the occurrence of menstrual cycles at intervals of less than 18 days. Polyhypermenorrhea is periods of heavy flow that occur more frequently than normal. Oligomenorrhea is defined as infrequent menstrual periods, the interval between periods being 40 to 45 days. Metrorrhagia, or intermenstrual bleeding, is uterine bleeding at any time other than during the menstrual period. Irregular cycles may be defined as variations of more than 5 days in an individual woman's cycle length. Women older than 40 generally have shorter cycles, and 7 years before menopause the incidence of abnormally short or long cycles increases. In a study of 1,560 nurses, Shortridge (102) found that the proportion of women reporting cycles of fewer than 25 days was 4.4% for women aged 30 to 34 years but increased to 8.2% at 40 to 45 years.

One bleeding pattern is excessive flow, referred to as menorrhagia or hypermenorrhea. To quantify the amount of flow, the number of menstrual pads or tampons used may be counted. A menstrual pad and a tampon are considered saturated when they contain 30 to 50 mL and 20 to 30 mL of blood, respectively. The number of pads used per day can be a measure of hypermenorrhea, although because of variability in women's hygiene practices this measure can be fairly inaccurate. During the first 2 days of her period, a woman usually uses three to six pads or tampons per day; if more than six pads or tampons are used or if clots are present, the flow may be abnormally heavy. Dysmenorrhea, or painful menstruation, is recognized as symptoms that are sufficiently severe to cause loss of time from work or school. These symptoms may include lower abdominal cramping, backache, aching thighs, nausea, diarrhea, headache, anorexia, irritability, and poor concentration. Primary dysmenorrhea is unrelated to an obvious physical cause while secondary dysmenorrhea is linked to pelvic disease. In a population of 293 workers, it was found that the baseline prevalences of secondary amenorrhea, dysmenorrhea, secondary amenorrhea, intermenstrual bleeding, and hypermenorrhea were 7.9%, 14.0%, 16.4%, and 28.3%, respectively (103).

Studies of the effects of exposure on menstrual function must account for the myriad risk factors associated with these conditions. The association of anorexia nervosa and amenorrhea is well-known and appears to entail a decrease in the ratio of body fat to lean body mass. Vigorous exercise, such as long-distance running, dancing, gymnastics, tennis, skiing, rowing, or fencing, is associated with amenorrhea or oligomenorrhea. Women who have not borne children are at greater risk for dysmenorrhea and amenorrhea, and female genital tract disease and systemic illnesses also may cause menstrual disturbances. Contraceptive methods also influence the cycle. Smokers are at risk for both amenorrhea and dysmenorrhea, and a dose-response relationship between environmental tobacco smoke exposure and dysmenorrhea incidence was found in a study of nonsmokers (104). A study of 2,912 military women found smokers had significantly prolonged and frequent menses, intermenstrual bleeding, and irregular menses after adjustment for other factors (105). Another study of 309 women in which daily hormone measures across five menstrual cycles were used to define menstrual outcomes identified statistically shortened mean follicular phase lengths in women older than age 35 (106). Amenorrhea is also associated with alcoholism. When women stop drinking their menses return. Age is a well-established influence on menstruation related to the risk for irregular cycles for young girls and older women, and younger women are more likely to suffer from dysmenorrhea. Age at menopause, which has been associated with parity and irregular cycles, may also be influenced by environmental factors such as smoking, oral contraceptive use, socioeconomic adversity in childhood or adulthood, dieting or poor nutrition, and emotional stress, but heredity has been estimated to account for roughly half of the variation.

Attempts to assess relationships between occupational exposures and alterations in the menstrual cycle or the hormones that govern it are still relatively uncommon. Although menstrual disorders are frequently viewed as less serious than many health endpoints, the financial impact is high. National cost estimates for work loss due to heavy menstrual flow were estimated at $1,692 per woman year 2000 wage estimates (107). Furthermore, menstrual or hormonal disorders may reflect or suggest risks for other disorders, including subfecundity, early miscarriage, breast cancer, reduced bone density, or cardiovascular disease.

Historically, occupations associated with exposures to formaldehyde (108), and various solvents such as percholoethylene (109), have shown associations with menstrual disturbances in some, but not all outcomes, that is, principally associated with abnormal bleeding. More recently, altered cycle lengths were significantly associated with benzene exposure of more than 7 years among 3,434 married petrochemical workers in China who were potentially exposed to mixtures of solvents and other chemicals (110). Another analysis of the same industry in China found a significant increase in prolonged cycle lengths associated with solvent exposure (111). A study

of menstrual disorders among U.S. Air Force women found that fuel handling and abnormal cycle length approached significance with both dysmenorrhea and abnormal cycle length (112). In a subgroup of these women with valid urine samples, a significant inverse relationship was identified between exposure to aliphatic hydrocarbons measured in breath and preovulatory LH levels measured in urine (113). Significant differences in urinary hormone and hormone metabolite levels according to race were also seen in that study (114). Dry cleaning work with exposure to solvents was associated with a significant excess of menstrual disorders, including cycle length, menorrhagia, dysmenorrhea, and premenstrual syndrome (109). Manufacturing or handling certain drugs may also affect menses. Estrogen plant workers had increased intramenstrual bleeding (115), and nurses who handled cytotoxic drugs (102) had irregular menses compared with controls, but a study of female pharmacists who handled antineoplastics did not find such an effect (116). Table 12.2 summarizes the reported potential causes of menstrual disorders associated with environmental exposures and other known risk factors.

Exposure to physical hazards has been linked to abnormal menses, including irregular menses in women who experienced occupational shift work (117). One study found no effect of shift work on cycle length, duration, or flow (118). Women who work as airline flight attendants experience a variety of menstrual disorders (119), and multiple possible causative factors have been proposed, for example, vibration, disruption of circadian rhythms, altitude changes, and solar radiation. Menstrual function, however, was reported to revert to preflight status with longer jet flight experience (120).

The effect of job-related stress has been tied to menstrual disorders. A study of military women found a significant association between cycle length, hypermenorrhea, dysmenorrhea, and life event stress but not job stress (112). Prolonged cycles have also been demonstrated in nurses in high stress units and with high perceived stress or strenuous activity (121). Conversely, the risk of shortened cycles was found to be doubled among women in stressful jobs (122).

There are challenges present in undertaking investigations of menstrual disorders in working populations. Levels of effort can extend from collecting a one-time questionnaire to using daily logs with daily reproductive endocrine measurements. When menstrual history information is collected using questionnaire data, some studies have shown poor reliability. In one study of semiconductor fabrication workers, women who recorded cycle length information at baseline interview and in prospective diaries showed fairly accurate recall of cycle length, and the recalled information enabled regular and irregular cycles to be distinguished (123). In a survey of nurses, some menstrual-related variables had high reliability, including age at menarche and menopause, history of severe irregularity, uterine fibroids, ovarian cysts, endometriosis, pelvic inflammatory disease, and use of oral contraceptives and intrauterine devices (IUDs) (102). The variables that had fair to poor reliability were dysmenorrhea, hypermenorrhea, clotting, and spotting. Methods to improve data collection include restricting the history to a very recent time frame (say, the previous 3 months) or having the patient keep a daily log. A study of nurses, however, has shown that compliance with log keeping can be poor (118). Urine hormone measures could be used as an objective measurement of dysfunction or as a validity measurement, at least in a subpopulation keeping the daily diaries. Decisions must be made about the appropriateness of including or excluding persons who have risk factors that are known to strongly influence menses: use of hormonal contraceptives or an IUD, recent pregnancy, hysterectomy, primary amenorrhea, history of cancer of the reproductive organs, and age older than 40 years. One study of 1,535 women found that 49% of the workforce had one or more of these conditions (103); in another, 70% were excluded for similar reasons (109). The choice of exclusion criteria may impact recruitment of women from demographic subgroups when rates of exclusionary factors vary among targeted subgroups. For example, hormonal contraceptive use varies by racial group in the United States, therefore, alternative sampling or analysis design strategies may be indicated to improve representativeness when this exclusion is employed.

ASSESSING MALE EXPOSURES AND REPRODUCTIVE OUTCOMES

As described in Table 12.3, alterations in male reproductive capacity are quantifiable using biomarkers of testicular and post-testicular (epididymal, vas deferens, accessory sex gland related) events, neuroendocrine profiles, and tools for assessment of sexual function. Many sperm and semen biomarkers are currently available to provide information on the potential effects of toxicants. The WHO has published norms and standards for optimal collection, laboratory quality control, and analysis of traditional semen parameters (124). In contrast to methods frequently employed to study female-mediated exposure outcomes, most studies of male-mediated outcomes have explored exposure effects on male gametes due, in part, to their relative accessibility. The risk of an adverse fertility, pregnancy, or birth outcome due to a toxic sperm insult may go undetected unless it affects a high proportion of the sperm, or the damage to the sperm or its milieu exceeds a critical threshold. Plus, given the site and timing of insult, varying effects may be hypothesized.

Table 12.2
A Summary of Risk Factors Associated with Female Hormonal and Menstrual Disorders

Risk Factors	Amenorrhea, Oligomenorrhea	Hypermenorrhea, Polymenorrhea	Irregular Cycles/ Metrorrhagia	Dysmenorrhea	Other/ Unspecified
General					
Age			×	×	
Anorexia nervosa, underweight	×				
Obesity	×			×	
Pregnancy	×	×	×		
Lactation	×				
Nulliparity	×			×	
Female genital tract disorder					
Anatomic abnormality				×	
Endometriosis				×	
Polyps, fibroids		×	×	×	
Infections	×	×	×		
Chronic pelvic inflammatory disease				×	
Cancer of ovary, uterus, vagina	×	×	×		
Asherman's syndrome	×	×		×	
Systemic illness					
Hemorrhagic disorders		×	×		
Iron deficiency		×			
Systemic lupus erythematosus		×			
Diabetes	×				
Crohn's disease	×				
Hypopituitarism	×				
Cushing's syndrome	×				
Stroke	×				
Sarcoidosis	×				
Pituitary lesions	×				
Acute febrile illness	×				
Renal disease	×	×	×		
Liver disease	×	×	×		
Hypothyroidism		×	×		
Hyperthyroidism	×				
Multiple sclerosis	×				
Tuberculosis	×				
Medications					
Anticoagulants		×			
Excessive use of aspirin		×			
Tranquilizers, sedatives	×				
Steroids	×				
Phenothiazines	×				
Long-term tetracycline	×				
Spironolactone	×				
Injectable triamcinolone					×
Methaqualone					×
Contraceptive methods					
IUDs		×	×	×	
Oral contraceptives	×		×		
Tubal ligation		×		×	
Socioeconomic and psychological factors					
Stress	×	×		×	
Life events		×		×	×
Dissatisfaction with work				×	
Unmarried, separated, divorced status	×			×	
City dwellers	×				
Smoking (passive or active smoking)	×	×	×	×	
Alcohol abuse	×			×	
Vigorous exercise	×				

(*continued*)

Table 12.2 (continued)

Risk Factors	Amenorrhea, Oligomenorrhea	Hypermenorrhea, Polymenorrhea	Irregular Cycles/ Metrorrhagia	Dysmenorrhea	Other/ Unspecified
Occupational toxicants exposure					
Antineoplastics	×		×		
Tobacco					×
Fluorine					×
Weaving-industry compounds			×		
Cotton/textiles-industry compounds		×			×
Formaldehyde				×	×
Hormones	×		×		×
Carbon disulfide		×			
Benzol (benzene)					×
Vibration		×		×	
Croton aldehyde		×		×	
Petrol		×			×
Jet fuel					
Jet air travel	×	×	×	×	
Trinitrotoluene	×	×	×		
Solvents	×	×	×	×	
Clorophene					×
Cadmium					×
Shift work			×	×	
Superphosphates			×		
Perchloroethylene			×	×	

IUD, intrauterine device.
Inclusion of an exposure on this list does not necessarily imply an association with hormone or menstrual outcomes is well-established.

Table 12.3
Assessment of Male Reproductive Capacity in Humans

Method of Assessment	Neuroendocrine Effects	Effects on Testes	Posttesticular Events[c]	Sexual Function
Gonadotropins[a]	✓	—	—	—
Gonadal hormones[b] and others[c]	✓	—	—	—
Sperm density	—	✓	—	—
Sperm morphology and morphometry	—	✓	✓	—
Sperm motility (% motile and velocity)	—	✓	✓	—
Sperm viability (vital stain & HOS[d])	—	—	✓	—
Semen volume	—	—	✓	—
Semen Ph	—	—	✓	—
Marker chemicals from accessory glands	—	—	✓	—
Sperm function assays[e]	—	✓	✓	—
Sperm genetic analyses[f]	—	✓	✓	—
Penile biothesiometry	—	—	—	✓
Nocturnal penile measurements	—	—	—	✓
Personal history[g]	✓	✓	—	✓

[a]LH, FSH
[b]Testosterone, inhibin B; others: prolactin, thyroid hormone
[c]Includes production of seminal plasma components by sex accessory glands and maturation of sperm in the epididymis
[d]HOS, hyperosmotic swelling
[e]Includes acrosome reaction, hemizona assay of sperm binding, and sperm penetration assays
[f]Includes sperm chromatin structure assay, the acridine orange test, Comet, terminal deoxynucleotidyl transferase-mediated dUTP-biotin end-labeling; HPLC assessment of oxidative damage by 8-hydroxy-2-deoxyguanosine (8-OhdG) and DNA adducts, electron microscopy, enzyme-linked immunosorbent assay, and fluorescent in situ hybridization assessment of chromosomal aberrations
[g]Including pubertal development, paternity (pregnancy timing and outcomes), and sexual function (erection, ejaculation, orgasm, and libido)
Adapted from Schrader S, Kesner J. Male reproductive toxicology. In Paul M, ed. *Occupational and environmental reproductive hazards. A guide for clinicias.* Baltimore, MD: Williams & Wilkins; 1993 and Moline JM, Golden AL, Bar-Chama N, et al. Exposure to hazardous substances and male reproductive health: a research framework. *Environ Health Perspect.* 2000;108:807 with permission.

Spermatogenesis is a process wherein the germ cell proceeds through a series of (a) mitotic divisions for cell proliferation, (b) meiotic divisions generating genetic diversity and decreasing the chromosome number by half, and (c) differentiation steps antecedent to the release of immature spermatozoa from the testes. As sperm are transported through the epididymis, maturational changes occur, and full motility and fertilization ability is acquired. The process of spermatogenesis requires approximately 70 days in the human testis, therefore, the window of time between exposure and expression of an event may be relatively brief for acute events. There is a mixing of sperm during storage, so ejaculates contain sperm of different ages. Any one of the developing cell types, from testicular spermatogonia, spermatocytes, and spermatids, to immature and mature epididymal spermatozoa, may be susceptible to toxic exposures. For nonmutagenic events the most likely outcome associated with insult to the spermatogonia (stem cell) may be cell death and phagocytosis. Although cell death also may occur in later stages (i.e., the mature forms, spermatids and spermatozoa), the rapidity and efficiency of phagocytic processes are uncertain. The most sensitive endpoint is speculative. A likely scenario is that perturbing of the biochemical milieu in which the mature cells are maintained may be reflected initially as alterations in motility, followed by decreases in viability, leading to cellular degeneration and eventually decline in concentration. The measure of genetic damage may also be suggested by laboratory assays of sperm DNA damage and chromosomal derangements, or a damaged conceptus. Sperm assays, therefore, provide both a direct measure of male reproductive impairment and potentially an indirect measure of potential transmission of genetic damage to progeny.

The advantages and limitations of semen measurements for detecting occupational causes of reproductive impairment are summarized elsewhere (125,126). The advantages are that a large number of sperm cells can be collected, effects can be detected in workers who are not attempting to conceive (e.g., single men), and early detection may be possible when no alteration in fertility is apparent. The limitations include the challenge of obtaining a high participation rate, the potential for selection bias, and the large amount of biologic and measurement variability in certain sperm tests.

Other measures of potential damage may include reproductive hormone levels in men. Hormones are measured to assess effects of exposure on the integrity of the male neuroendocrine system. An intact hypothalamic-pituitary-testicular axis, as measured by hormonal levels, may provide a measure of the successful integration of the male reproductive system. To summarize the male neuroendocrine system, the hypothalamus integrates signals from the testes and the CNS to modulate its secretion of the gonadotropin-releasing hormone into the portal vasculature. This process drives the anterior pituitary gland secretion of the two gonadotropins, LH and FSH, and prolactin. The gonadotropins act on the Leydig, Sertoli, and germ cells to regulate spermatogenesis and testicular hormone production. Synthesis and release of testosterone is controlled by LH acting on the Leydig cells. FSH stimulates aromatization of testosterone to estradiol in the Sertoli cells. Inhibin is primarily produced by gonadal Sertoli cells and has recently emerged as a marker of spermatogenesis (127). Testicular endocrine secretions of testosterone, estradiol, and inhibin, and peripheral conversion of testosterone to estradiol, exert negative feedback on the hypothalamus and anterior pituitary gland to regulate gonadotropin secretion.

Although biomarkers of the reproductive endocrine axis and semen are the most common endpoints in male reproductive studies, an increasing number of studies are examining other outcomes, such as sexual function and postcoital outcomes. Personal reproductive histories have generally been used to assess sexual function, but nocturnal penile measurements provide more objective evidence of organic impairment. For postcoital outcomes, assessment of male as well as female exposures enables examination of the male-mediated effects of toxicant exposures at the level of the couple (e.g., TTP) and their offspring. Interview of male workers' wives is advantageous in studies relying on recall of past birth outcomes, as women reportedly have higher recall of dates for certain events, such as miscarriage (128). Increasingly, paternal effects are evaluated in studies of TTP (129–131), pregnancy, and birth outcomes (74,132) and studies of the subsequent developmental and disease status of their children (133).

When examining paternal effects, linking the exposure with the time of conception can be crucial. Obtaining precise identification of the specific exposure period that initiated the event is important to minimize misclassification errors. When pregnancy outcomes for the partners of an exposed male worker are assessed, the period of exposure just prior to conception (perhaps the preceding 4 to 6 months) or at conception is often used. Hence, it may not be a worker's total person-years of exposure that are important but the exposure that occurred relative to a critical period of reproductive development (134). Interpretation of the male versus female origin of an adverse reproductive outcome may be clouded if exposure is incurred indirectly by the presumably nonexposed partner. For example, exposure hypothetically could occur from contact with a partner's contaminated skin or work shoes and clothes, from sidestream inhalation of breath when a toxicant is off-gassing, or a female partner's contact with semen containing toxicants the male encountered. In a recent review, however, Klemmt and Scialli (135) concluded that exposures of women or conceptuses to clinically important levels of xenobiotics via semen is unlikely unless male exposures were extremely high, as by the most liberal estimate, levels in maternal

Table 12.4
Some Occupational and Environmental Exposure Variables Presented in the Human Research Litrature on Reproductive Outcomes in Adult Men

Variables[a]	Reproductive System Outcomes			
Past or current exposure to:	Semen analysis parameters (sperm count or density, abnormal shape, altered sperm transfer, etc.)	Sperm genetic integrity (DNA or chromosomal)	Reproductive hormones	Sex organs or sexual performance
Energy	✓ (e.g., heat [welding, saunas, laptops]	✓ (e.g., ionizing radiation)	✓ (e.g., heat, ionizing radiation)	✓ (e.g., ionizing radiation, stress, alcohol)
Lifestyle factors	✓ (e.g., alcoholism, smoking [tobacco], stress, diet)	✓ (e.g., alcohol use, smoking)	✓ (e.g., alcoholism, smoking)	✓ (e.g., smoking)
Metal(s)	✓ (e.g., aluminum, brass, cadmium, chromium, lead, manganese, mercury vapor, nonphysiologic zinc, welding–mild or stainless steel)	✓ (e.g., lead)	✓ (e.g., cadmium, chromium electroplating and welding, lead, manganese, mercury vapor, selenium)	✓ (e.g., cadmium)
Pesticide(s)	✓ (e.g., alachlor/metachlor, carbaryl [Sevin], 2,4-D acetic acid, ethylene dibromide, organochlorines [kepone, DDT], organophosphates [diazinon, ethylparathion/ methamidophos], cholinesterase inhibitors, DBCP, bromine vapor, fenvalerate, dioxin, herbicides)	✓ (e.g., carbaryl, organophosphates, [chlorpyrifos, ethylparathion/ methamidophos, parathion], DBCP, fenvalerate, dioxin)	✓ (e.g., organophosphates, DBCP, dioxin)	✓ (e.g., kepone, DBCP)
Pressure				✓ (e.g., occupational bicycling)
Solvent(s)	✓ (e.g., aromatic hydrocarbons [benzene, toluene, xylene, ethylbenzene], 2-bromopropane, methylene chloride, styrene and acetone, perchloroethylene, trinitrotoluene, trichloroethylene)	✓ (e.g., benzene, carbon disulfide, ethylene glycol monoether, styrene)	✓ (e.g., carbon disulfide, styrene, toluene, trinitrotoluene, trichloroethylene)	
Misc. chemical(s)	✓ (e.g., phthalates [monoethyl, monobutyl, monobenzyl, esters], (PCBs)	✓ (e.g., monoethyl phthalate, PCBs)	✓ (e.g., PCBs, stilbene derivative [DAS], synthetic estrogen/ progestin [manufacture])	✓ (e.g., DAS)

[a]Variables may be of potential interest, for example, as descriptors, exclusions, covariates, confounders, matching criteria, or for outlier or results interpretation in some studies. Relevant information may include specific exposure(s), dose, duration, latency, and for sperm parameters, timing in relationship to sperm cycle.
DBCP, 1,2-dibromo-3-choloropropane; DDT, dichlorodiphenyltrichloroethane; PCB, polycholorinated biphenyl; DAS, 4,4'-diaminostibene-2,2'-disulfic acid; a stilbene derivative.
Inclusion of an exposure on this variable list does not necessarily imply an association with male reproductive system outcomes has been established.

blood and the conceptus by this route would be three or more orders of magnitude lower than in the blood of the exposed male partner.

Human studies on occupational hazards to male reproduction are reviewed elsewhere (9,136). Table 12.4 lists some environmental and occupational factors that have been the subject of reproductive studies in adult men or in vitro work using human sperm. Some of these factors may be important to consider when designing or evaluating a study as: matching or exclusion criteria; potential confounders; or effect modifiers, or for outlier or results interpretation. Although the scope of factors listed is fairly broad, there is currently a paucity of human research on most of them. Where multiple human studies have been done, the results for some factors are inconsistent. The strength of current evidence regarding such factors must be weighed when determining what data is appropriate to collect or when evaluating the methods and findings of published studies. Relevant considerations regarding these factors may include specific exposure(s), dosage, duration, latency, and for sperm parameters, timing in relationship to the sperm cycle.

The first specific reports on reproductive effects of an industrial chemical appeared in the late 1800s and concerned lead toxicity. These studies may still be quite pertinent in developing countries where higher exposures are not uncommon (137). Findings in an occupational lead exposure study in the United States by Lancranjan et al. (138) in 1975 indicated that absorption of moderately increased amounts of lead resulted in asthenospermia, hypospermia, and teratospermia. Animal studies reported similar findings. Since that time, many, but not all, studies of inorganic lead exposure have found adverse effects on semen parameters associated with lower concentrations, together with effects on the reproductive endocrine axis and male-mediated fecundity (139–142). Recent findings suggest adverse effects on sperm quality may be seen at low concentrations (143). Lead exposure may also produce other reproductive effects, such as oxidative DNA damage, perturbed chromatin condensation, altered acrosome reactions, and decreased prostate secretory function (144–146). Results of a few recent analyses of TTP among partners of men occupationally exposed at levels below 50 μg per dL have been mixed (129–131,147). Future prospective studies of lead workers with input regarding TTP from female partners regarding recognized conceptions or measurement of hCG levels to detect unrecognized ones might yield additional insight into this important question. Subsequent to the identification of lead as a reproductive toxicant, workplace studies of welders and other metal workers as well as other groups of men with environmental exposures, have suggested other metals may also have male reproductive effects.

It was not until the late 1970s, after workers' exposure to DBCP was noted to have a striking effect on reproduction (148), that male occupational reproductive effects became a serious concern. In 1981, shortly after the DBCP study, the Occupational Safety and Health Administration (OSHA) proposed a revision of the existing allowable exposure standard for workers exposed to EDB, based on health effects data that included information from animal studies reporting adverse male reproductive effects (149). Several years later, OSHA reduced the permissible exposure limits for EDB, and the U.S. Environmental Protection Agency banned its use in most agricultural applications, such as in soil fumigants, while its use as a scavenger in leaded gasoline declined in the United States with the ban on leaded gas. Subsequently, human studies have demonstrated relationships between EDB exposure and adverse effects on sperm quality among workers (150,151). A number of other studies have since examined associations between exposure to various pesticides or agriculture work and male reproduction. Conception delays were significantly increased among male greenhouse workers (152), and statistically nonsignificant delays were reported by male dichlorodiphenyltrichloroethane applicators (153). Some previous studies of specific pesticides or mixtures have shown male endocrine or semen quality changes, including lowered sperm counts and densities, and altered sperm motility, morphology, and genetic integrity as well as other semen parameters. An increased risk of sperm genetic damage has been shown in two studies of organophosphate (OP) pesticide-exposed workers in the absence of a significant relationship between exposure and traditional semen analysis parameters. Genetic damage was defined by significantly increased rates of aneuploidy in the sperm of Chinese OP pesticide workers using the fluorescence in situ hybridization, or FISH (154), and by significantly increased total sperm aneuploidy and sex null frequencies among a subgroup of Mexican OP exposed sprayers and other agricultural workers (155). Significantly increased sperm choromatin structure assay (SCSA) alterations were also found in the sperm of the Mexican agricultural workers, suggestive of impaired sperm chromatin condensation (156). Similarly, exposure to the fungicide fenvalerate was associated with significant levels of genetic instability, as measured by SCSA, terminal deoxynucleotidyl transferase mediated dUPT nick end labeling (Tunel), Comet, and the FISH assays of chromosomal derangements in Chinese pesticide factory workers (157). Relationships between sperm SCSA and FISH results and pesticide-spraying Danish farmers compared with controls, however, were not significant (158,159). Thus, assays of sperm genetic integrity and stability also appear to provide additional information about male fertility beyond those provided by traditional semen parameters (160,161) and have been increasingly applied in occupational studies.

Evidence is mounting that high levels of sperm with altered genetic integrity perhaps contributes to reduced

fecundity and infertility. It has been estimated that fecundity decreases when more than 30% to 40% of spermatozoa are identified as having DNA instability by SCSA (162), although not all studies support this finding (163). Impairments in fertilization, blastocyst development, and pregnancy rates have been linked to sperm genetic damage in studies of in vitro fertilization and intracytoplasmic sperm injection outcomes. Much of the infertility evidence is from studies that have demonstrated significantly increased levels of genetic damage among men attending infertility clinics compared with men who are fertile. These results suggest that sperm genetic integrity assays may help elucidate the mechanisms underlying some adverse male-mediated reproductive outcomes. Experimental evidence from rodent and in vitro studies raises questions regarding the transmissibility of certain toxic insults to future generations through heritable germ cell genetic effects (164,165) or epigenetic mechanisms (166). Much remains unknown regarding mechanisms of suspected paternally mediated effects on offspring, such as spontaneous abortions, developmental disorders, and possibly childhood cancers (167).

Solvents are a persistent concern because of the common use of these compounds both in the workplace and at home. A recent metaanalysis of 14 studies of paternal organic solvent exposure and spontaneous abortions and major malformations found an increased risk for neural tube defects, but not spontaneous abortions (62). No increase in TTP was found among solvent-exposed men in a study in which exposure was recalled retrospectively (168), while reported delays in recognized first conceptions, but not later conceptions, were found in a study that used biomarkers to help characterize solvent exposure (16). Semen and sperm abnormalities, and altered hormone levels, have been linked to a number of different solvent exposures (Table 12.4). As with many other exposures, specific solvents may be encountered as mixtures with other solvents or agents, such as pesticides, and multiple solvents may be used by an individual for different applications. Aircraft maintenance workers, for example, work in a solvent mixture milieu. Lemasters et al. (169) measured levels of individual solvents among these workers in both air samples and exhaled breath (internal dose). No relationships were found between internal dose of solvents and postemployment spermatogenic changes; however, statistically significant declines in sperm motility of 19.5% were seen in a subgroup (paint shop workers). When feasible, measurement of panels of validated biomarkers is useful, as these measures permit current exposures to be characterized both as mixtures and as individual chemicals and also provides additional dose information. This strategy enables improved adjustment for other potentially confounding and modifying co-exposures during analysis and enhances statistical power to detect effects of individual chemicals. In general, although studies of potential reproductive effects of exposure of men to solvents as a group have been published, studies of specific agents included under the heading of "solvents" are few, as is true for most of the agents described in Table 12.4.

In summary, workers may experience a range of physical or chemical exposure, from brief but extremely high to continuous low-level exposure, and the response may depend on several factors. Therefore, the choice of study design, the decision to collect biologic semen samples or to use survey methods to characterize exposure, and appropriate survey content will vary, depending on the type, timing, and duration of exposure and the population and outcomes to be studied. The survey approach may be better suited to examination of historic exposures unless these have been constant over time. Although survey approaches were shown to be as sensitive as use of biologic samples when exposures were very potent (e.g., with DBCP) (148), these methods are probably not sufficiently sensitive for detecting more subtle effects of subfecundity.

CHALLENGE TO HEALTH PROFESSIONALS

Although more than 75,000 industrial chemicals are produced or imported into the United States with many new ones being introduced annually (170), only a small fraction have been evaluated in model species for reproductive toxicity potential. Far fewer have been evaluated in human studies. Moorman et al. (171) prioritized for future field studies a subset of 43 chemicals for which animal reproductive toxicity was found at relatively low doses, yet a paucity of human data existed. Chemicals were ranked on the basis of potential for worker exposure and reproductive toxicity in animals. The focus of animal studies is to quantify dosages and conditions that produce toxicity rather than crudely define exposures as "toxic" versus "nontoxic." When estimates of risks to workers from a given level of exposure are based on extrapolation of animal study results, additional uncertainty is introduced, even when appropriate animal models are used. Despite this uncertainty, animal evidence is discounted at the peril of repeating the 1,2-dibromo-3-chloropropane (DBCP) experience of failing to prevent worker exposure to a potent hazard that was identified in animals years earlier (172). Where regulatory and recommended exposure limits are available, they are frequently based on nonreproductive outcomes when other targets such as the liver, kidney, and CNS are considered relatively more sensitive. For example, OSHA regulatory limits were available for only 14 of the 43 chemicals ranked by Moorman et al. (171), and these limits were based on nonreproductive endpoints. When regulatory limits have not been established for an exposure of concern, awareness of whether

this is a result of paucity of data, inconsistent data, or an established lack of associated risk is important. Workers seeking counsel from clinicians should be advised of both known reproductive risks and the unknown nature of their risk when information is uncertain or lacking.

Clinicians should collect occupational histories from their patients. Relevant information includes not only chemical exposures but also biologic and physical agents, physical demands, and psychological stressors that may impact reproductive health. Useful information is also obtainable from worksite employee health personnel and consultation with occupational health specialists. Whether practicing in industrial or other clinical settings, clinicians face the challenge of evaluating the level of work-related risk, sometimes in the face of incomplete knowledge about actual exposures and risks. Material safety data sheets (MSDSs) are a valuable source of information about workplace chemicals for which employee access is required by law in the United States, but these may not list all ingredients nor adequately address reproductive risks. Paul and Kurtz (173) found that less than half of the nearly 700 MSDSs supplied by central Massachusetts companies for products containing two established reproductive toxicants, lead or ethylene glycol, provided information regarding reproductive risks. When workers' exposures are known, the task of retrieving current reproductive risk information about these is facilitated by using Internet resources developed to provide reproductive and developmental toxicity information. Polifka and Faustman (2002) published a useful review of these resources, which provides information on access, content, and context for various sites, such as Reprotox, Reprotext, Teratogem Information System, Shepard's Catalog of Teratogenic Agents, Reprorisk, and others (174). New and emerging research and surveillance tools may yield clearer insights into risks and mechanisms of human toxicant exposures. Among these newer tools, summarized by Lawson et al., are exposure databases, geographic information systems, the National Institute for Occupational Safety and Health Standardized Occupation and Industry Coding systems software for assignment of industry and occupational codes, biomarkers of exposure and effect, structure-activity prediction, high throughput assay-based technologies, and bioinformatics in genomics and proteomics (175).

Promoting reproductive health in the workplace requires a proactive approach. A study of the use of reproductive consultation services at two occupational health clinics found that of 51 patients who had presented during the study period (1 man and 50 women), 10 wished to discuss a future pregnancy and 41 were already pregnant, with a mean gestational age of 10.9 weeks (176). The implication is that the reproductive health of all workers must be protected, as 50% of pregnancies are unplanned, and the dangers of workplace preconception and early pregnancy exposures will generally be incurred before a worker presents for consultation with a clinician. Unfortunately, most men and many women do not seek counseling about reproductive health hazards before they are encountered.

Workers should be informed of both their employer's maternity and paternity leave policies and legislation such as the Family and Medical Leave Act, the Pregnancy Discrimination Act, and applicable state laws in the United States and maternity protection laws in the European Union and other countries to assist them in making job decisions. Familiarity with laws regarding workers' rights and employers' legal responsibilities as these pertain to reproductive matters is crucial for clinicians in industrial settings.

The American College of Occupational and Environmental Medicine website currently lists guidelines for workplace management of reproductive and developmental hazards (7). These guidelines address occupational medicine issues, including the hierarchy of methods to eliminate or control and monitor worker exposure, risk communication, employer pregnancy notification, temporary reassignment, medical surveillance, breast feeding, and preventing contamination of workers' home environments.

Workplace programs established to improve the health of workers overall may also lower reproductive risks related to both work and lifestyle. Programs that successfully promote exercise, healthy diet, smoking cessation, stress management, recommended adult vaccinations, and health screening and referrals all have the potential to improve the reproductive fitness of workers who may conceive. Educational programs for women and their significant others who are pregnant or may be planning a pregnancy may also be an appropriate workplace offering. Organizations such as the March of Dimes and La Leche League International offer excellent educational materials, including brochures, videos, speakers, and generally high-quality teaching programs. New mothers and fathers may also benefit from policies that allow for leave to care for infants and that ease their return to the workplace. Management and labor need to work closely to ensure that the workplace is a safe environment for men and women and their unborn children, and that women who return to the workplace have had an adequate recovery period to do so with a minimum of physical burden.

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