ACTA FAC MED NAISS

UDC 611.61/.62-008:615.9

Professional article

ACTA FAC MED NAISS 2007; 24 (3): 135-141

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TOXIC AGENTS AND REPRODUCTIVE SYSTEM DISORDERS

SUMMARY

Because some research suggests that the reproductive system is more sensitive then other organ systems, it is important that exposure limits formulated in the future take reproductive toxicity into consideration. Numerous agents have been shown to have adverse reproductive or developmental effects. Structural chromosomal changes may have no adverse effects, or they may be associated with mental retardation, anomalies, reduced fertility, or malignancy. Increased frequencies of chromosomal aberrations have been reported in radiation workers and in workers exposed to chemicals such as benzene, styrene, ethylene oxide, epichlorohydrin, arsenic, chromium, and cadmium. Occupational agents can disrupt sperm production either directly, by injuring testicular cells, or indirectly, by interfering with the hormonal regulation of spermatogenesis. Toxic agents may also impair sexual function by reducing libido or by inhibiting erection and ejaculation. Toxicity to oocytes may occur from occupational exposure received by a woman worker. Exposure to toxic agents after the first trimester of pregnancy can still cause problems. Certain exposures may reduce fetal growth, result in functional or neurobehavioral abnormalities in offspring, or increase the risk of pregnancy complications such as preeclampsia or preterm birth. Health professionals can prevent or reduce work-related health risk through patient education and counseling and by advocating for workplace change to decrease or eliminate deleterious exposures.

Key words: reproductive system, workplace, toxic agents

INTRODUCTION

Reproductive processes in humans are complex and insufficiently understood. In a precisely regulated hormonal milieu, normal human reproduction proceeds from formation and transport of the germ cells through fertilization, implantation, and prenatal, and postnatal development. Toxic agents can act at one or many sites to disrupt this chain of events, resulting in reproductive dysfunction or adverse pregnancy outcomes.

Numerous agents have been shown to have adverse reproductive or developmental effects, although for many substances the available evidence is limited to studies in experimental animals. Most workplace exposure limits were formulated to protect against adverse health outcomes other than reproduction, such as acute toxicity or cancer. Because some research suggests that the reproductive system is more sensitive than other organ systems, it is important that exposure limits formulated in the future take reproductive toxicity into consideration (1).

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Genotoxicity

Genotoxicity can occur in either men or women. Most numeric chromosomal abnormalities are incompatible with survival. Infants born with chromosomal abnormalities often have physical, behavioral, and intellectual impairments. Structural chromosomal changes may have no adverse effects, or they may be associated with mental retardation, anomalies, reduced fertility, or malignancy.

With the use of bacterial assays, increased mutagenic activity has been detected in the urine of workers exposed to such substances as anesthetic gases, chemotherapeutic agents, and epichlorohydrin. Increased frequencies of chromosomal aberrations have been reported in radiation workers and in workers exposed to chemicals such as benzene, styrene, ethylene oxide, epichlorohydrin, arsenic, chromium, and cadmium. Although these assays are useful as biologic markers of exposure to genotoxicants, they do not predict specific reproductive health effects in individual workers.

The risk of adverse pregnancy outcome after preconception exposure of men to toxic agents is an area of active research. A number of mechanisms have been postulated for these male-mediated effects, including germ cell mutagenesis. Although findings have yet to be replicated or precisely clarified mechanisms, increased rates of pregnancy loss have been reported among the wives of men exposed to lead, inorganic mercury, organic solvents, and other agents (Table 1). Some studies suggest that certain paternal occupations pose an increased risk for congenital occupations and childhood cencers, but more research is needed to explore this issue (1,2).

Spermatogenesis

Alterations in sperm count or semen quality have been documented for a number of occupational exposures. Occupational agents can disrupt sperm production either directly, by injuring testicular cells, or indirectly, by interfering with the hormonal regulation of spermatogenesis. Toxic agents may also impair sexual function by reducing libido or by inhibiting erection and ejaculation. As long as the stem cell precursors are spared, spermatogenic damage may be reversible over time. This appears to be the case with most substances studied so far, although few substances have been studied thoroughly. Table 1 lists some occupational agents known or suspected to affect male reproductive function adversely.

Pesticides. Perhaps the best known spermatotoxin is dibromochloropropane (DBCP), the first substance discovered to cause infertility in American workers. Although the manufacture of DBCP has been banned in the United States, it remains a low-level groundwater contaminant in some states. Another pesticide, ethylene dibromide, has been associated with post-testicular effects, including decreased sperm velocity, motility, and viability.

Table 1. Selected occupational agents with suspected effects on male reproductive function

Adverse effects	Examples
Decreased libido, hormonal alteratios	Lead, mercury, manganase, carbon disulfide, estrogen agonists(e.g.,polychlorinated biphenyls and organohalide pesticides); workers manufacturing oral contraceptives
Spermatotoxicicity	Lead, dibromochloropropane (DBCP), carbaryl, toluenediamine and dinitrotoluene, Ethylene dibromide, plastic production (styrene and acetone), ethylene glycol monoethyl ether, welding, perchloroethylene, mercury, heat, military radar, Kepone, bromine radiation (Chemobyl), carbon disulfide, 1,4- dichlorophenoxy acetic acid (2,4-D).
Spontaneous abortion in partner	Solvents, lead, mercury; workers in rubber and petroleum industries
Altered sex ratio in offspring	Dibromochloropropane (DBCP)
Congenital malformations in offspring	Pesticides, chlorphenates, solvents; firefighters, painters, welders, auto mechanics, motor vehicle drivers, sawmill workers and workers in aircraft, electronics and forestry and logging industries
Neurobehavioral disorders in offspring	Alcohols, cyclophosphamide, ethylene dibromide, lead, opiates
Childhood cancer in offspring	Solvents, paints, pesticides, petroleum products; welders, auto mechanics, motor vehicle drivers, machinists and workers in aircraft and electronics industries

Heavy metals. Among the heavy metals, lead is the best-studied spermatotoxin. In investigations of workers exposed to lead in battery manufacture, blood lead levels (BLLs) higher than 40µg/ dL have been associated with decreased sperm counts and aberrant sperm motility and morphology. Evidence suggests that lead has a direct toxic effect on the gonads and may also act at the level of the hypothalamus and pituitary to impair endocrine function. Agents that affect the central nervous system or that cause severe debilitation may affect sexual function. For example, decreased libido has been associated with severe lead or manganese poisoning.

Glycol ethers. The ethylene glycol ethers, 2-methoxyethanol and 2-ethoxyethanol, and their acetates are organic solvents used in multiple industrial applications. These agents cause testicular atrophy and disruption of the seminiferous tubules in several laboratory animal species, and they have been associated with decreased sperm counts in exposed workers. The ethylene glycol ethers target meiotic spermatocytes; at high doses, effects on spermatogonia and late spermatids have also been reported. The ethylene glycol ethers are metabolized in the body to alkoxyacetic acid, which are responsible for their reproductive toxicity.

Hormonally active compounds. Gynecomastia and decreased libido have been reported in men involved in the manufacture of oral contraceptives. Some chemicals, such as the polyhalogenated biphenyls and organohalide pesticides, are structurally similar to the reproductive sex steroid hormones, raising the possibility that they could disrupt male reproduction by binding to endogenous hormone receptors. Several studies have suggested that average sperm counts in men have fallen during the past several decades, but adhere studies have not confirmed this finding. More research is needed to clarify the potential role of endocrine-disrupting chemicals on male fertility and reproductive outcomes (1,3).

Oogenesis

Toxicity to oocytes may occur from occupational exposure received by a woman worker. In addition, exposures received by a female fetus while her mother is working could theoretically affect her fertility during adulthood. In adults, disturbances in ovulation manifest clinically as infertility or menstrual dysfunction. Ovarian toxicity can result in premature menopause, as tobacco research has demonstrated.

Menstrual disorders have been reported among women in various occupations, including athletes and dancers, agricultural workers, and those formulating oral contraceptives. Reduced fertility has been reported in semiconductor workers and in dental assistants exposed to high levels of metallic mercury vapor or nitrous oxide. The probability of conception in each menstrual cycle was almost 60% lower among women exposed to unscavenged nitrous oxide for 5 or more hours per weak than among unexposed women (1,5,6).

Pregnancy

With rare exceptions, contemporary studies from industrialized nations reveal better pregnancy outcomes among women in the workforce compared with unemployed women. This finding may be related in part to the healthy worker effect and to the economic and health care benefits derived from the work experience. On the other hand, a number of work exposures may be associated with adverse pregnancy outcomes (Table 2).

Table 2. Selected occupational agents with suspected effects on pregnancy

Agent (illustrative exposures)	Reported effects
Physical agents	
Strenous work (standing >6hr/wk per shift, working>40 hr/wk)	Preterm delivery. Women with medical or obstetric conditions predisposing to preterm delivery may be at particular risk
Ionizing radiation (x-rays, radionucleotides such as P32)	At high doses, growth deficits, Cns malformations, mental retardation; possible low risk of genetic defects, childhood cancer at doses <5 rem.
Noise	Possible fetal hearing loss(beyond the fifth month of pregnancy),possible increased risk for preterm birth
Electromagnetic fields (fields derived from flowing electric currents)	No reproductive effects from fields generated by video display terminals; further research is needed on exposures of very high field strength.

Chemical agents	
Heavy metals	Neurobehavioral deficits in infants (with prenatal lead exposure, deficits reported at cord blood lead levels as low as 10-20μg/dL)
Organic solvents (glycol ethers, toluene, xylene)	Spontaneous abortion; fetal loss rates increased in semiconductor workers exposed to EGEE/EGM; modestly increased risk of birth defects for mixed solvent exposure; toluene abuse (fetal solvent syndrome)
Antineoplastic agents (cis-platin, doxorubicin, fluorouracil, methotrexate)	Spontaneous abortion
Other pharmaceuticals (anti-viralis such as ribaflavin; estrogenic or antiestrogenic compounds such as tamoxifen; imunosupressive agents such as cyclosporine)	Spontaneous abortion, sperm effects in male animals and teratogenesis in famale animals have been noted at high doses
Carcinogens and mutagens (ethidium bromide, alfatoxin B_1)	Human data limited; sperm effects noted in male animals, and terato-genesis and cancer in offspring of exposed female animals
Waste anestethic gases (nitrous oxide) (N_2O)	Spontaneous abortion
Sterilants and disinfectants (ethy-lene oxide, formaldehyde)	Spontaneous abortion
Polychlorinated biphenyls (PCB_s) (chlorodiphenyls, breast milk, low-lewel dietary exposure related to mild neonatal chlorobiphenyls)	Congenital PCB syndrome at high doses excreaded efficiently into growth and neurobehavioral deficits in some studies
Pesticides (organochlorines such as lindane; organopho-chloropyrifos; *n*-methyl carbamates such as carbaryl; fungicides such as benomyl; herbicides such as 2,4-D)	Both male and female reproductive effects have been noted in animal studies for a number of pesticides; there are also some sphates such as positive studies in workers; review data for each compound
Biologic agents	
Hepatitis B virus (HBV)	Neonatal carrier state; chronic liver disease and mortality
Human immunodeficiency virus (HIV)	Morbidy and mortality for infected pregnant women and neonates
Cytomegalovirus (CMV)	Neonatal death, malformations, developmental deficits; seroconversion rates in health care workers using adequate precautions not increased compared with community controls
Rubella virus	Spontaneous abortion, stillbirth, congenital defects with infection during first 16 wk of pregnancy
Varicella-zoster virus	Serious maternal pneumonia; malformation risk approximately 5% for infection in first half of pregnancy; neonatal morbidity/ mortality if maternal infection <5 days before or <2days after delivery

EGEE/EGME: ethylene glycol monoethyl ether/ethylene glycol monomethyl ether

The preimplantation phase of development is often referred to as the "all-or-none" period. This terminology derives from studies showing that sufficiently high doses of ionizing radiation may cause death of the conceptus, but sublethal doses are unlikely to result in teratogenic effects because of effective cellular repair processes.

The embryo (from the 17th to the 56th day after conception) is acutely sensitive to teratogenic insult. The second and third trimesters are marked by significant growth of the conceptus and by the continued differentiation and maturation of some organ systems. Therefore, exposure to toxic agents after the first trimester can still cause problems. Certain exposures may reduce fetal growth, result in functional or neurobehavioral abnormalities in offspring, or increase the risk of pregnancy complications such as preeclapsia or preterm birth.

Transfer of chemicals across the placenta occurs primarily by passive diffusion. Chemicals that are lipophilic and of low molecular weight cross the placenta readily. Clinical manifestation of developmental toxicity depend on the properties of the agent, the timing and dose of exposure, genetic susceptibility, and other factors. Some agents, such as thalidomide and diethylstilbestrol, affect the embryo at doses far below those that induce maternal toxicity. Other agents, such as methyl mercury and cyclophosphamide, are harmful to the conceptus only at doses that are toxic to the mother (1,7).

EVALUATION AND CONTROL OF PERSONAL RISK

Steps in the Clinical Work-up

Common clinical situations that require knowledge of occupational reproductive hazards include preconception counseling evaluation of the infertile couple, and assessment of workers who are pregnant or who have experienced an untoward pregnancy outcome. In all of these situations, it is essential to answer the following four questions:

To what agents is the patient potentially exposed?

Because reproductive disorders have multiple causes, the medical history, work history, and history of environmental exposures all help the clinician to assess the reproductive risk profile of a given worker. This information should be gathered for both the male and the female partner. Physical as well as chemical and biologic exposures should be noted. No physical findings are pathognomonic for work-related reproductive disorders; however, the examination may identify signs of exposure (e.g.dermatitis in a solvent-exposed worker) or pathology contributing to the problem (e.g. uterine fibroids in a woman with menstrual irregularity).

Is the patient actually exposed to the agents and, if so, what are the timing and dose of exposure?

Working with an agent is not necessarily the same as being exposed to the agent. Through the occupational history, the clinician can estimate whether the likelihood of internal body exposure to the agent is high, low, or negligible. The history can help to determine whether exposures are episodic or chronic in nature. Use of protective measures at work, such as engineering controls or personal protective equipment, may have reduced the exposure. Because teratogens exert their effects during specific critical periods of organogenesis, every effort should be made to establish gestational age at the time of exposure precisely. Abnormal semen parameters should prompt a search for gametotoxic exposures occurring several months before the onset of the problem, since spermatogenesis takes about two months to complete. Occasionally, exposures in the more distant past are important. For example, 90% of absorbed lead is stored in bone; conditions that increase bone turnover, such as menopause and perhaps pregnancy, may increase the BLL.

Worksite walk-throughs, the assistance of industrial hygienists, and the use of available biologic markers can greatly enhance understanding of actual exposures. However, in only a few instances in the United States have occupational standards been established with reproductive risks in mind (lead, ethylene oxide, DBCP, and ionizing radiation). Therefore, exposure data should not be considered simply in terms of whether regulatory limits are exceeded. The recommended exposure limits (RELs) promulgated by the National Institute for Occupational Safety and Health (NIOSH) do consider available data on reproductive and developmental effects, but they are not updated often.

Is there evidence to suggest that the agents cause adverse reproductive or developmental effects?

Even after a comprehensive history has been taken, questions frequently remain about the precise identity of chemicals handled on the job. Material safety data sheets (MSDSs) contain essential information about hazardous product ingredients and should be carefully reviewed. However, reproductive and developmental toxicity data on the MSDSs may be sparse or missing entirely. Additional data on reproductive and developmental

toxicities of occupational agents are available from computerized databases, toxicology hotlines, reference books and government agencies.

Given the information collected, doses the patients exposure to the agents pose a reproductive or developmental risk.

The final step in the work-up involves assimilating exposure and health effect data to estimate the degree of risk to the patient. In addition to the properties of the agent and the characteristics of the exposure, the health professional must consider biologic factors that modify risk, such as age, nutritional status, and preexisting medical or reproductive problems. For example, the risk of fetal chromosomal abnormalities increases in women 35 years of age and older. Cigarette smoking is associated with subfertility, earlier age of menopause, spontaneous abortion, and fetal growth deficits. Not every reproductive problem is work-related. On the other hand, the presence of a personal risk factor does not rule out contribution by a work exposure (1,8,9).

Prevention

Intervention is clearly warranted when exposure to any chemical or physical agent exceeds regulatory exposure limits. Because few legally mandated exposure limits are designed to protect against reproductive system effects, exposures at or below mandated limits deserve attention when the agent is a known or suspected reproductive hazard. Health professionals can prevent or reduce work-related health risk through patient education and counseling and by advocating for workplace change to decrease or eliminate deleterious exposures.

RISK MANAGEMENT

Once the risk assessment and risk communication have occurred, risk management completes the sequence. In order of priority, the following actions may be considered for a given reproductive hazard situation (1). Exposure reduction or elimination: replacement of hazards with safer agents; improved engineering controls; safer work practices; and personal protective equipment. Exposure reduction or elimination in the most desirable option should be attempted in all situations involving a reproductive hazard (2). Temporary job transfer: Remove an individual from work environment in which reproductive hazard exists. Problems may occur when there is no non-exposed job location. Transfer needs to occur before conception (which is not always planned) and this may require a written request from the personal physician (who may not be familiar with the work setting). Thus, this option should be considered when there is a high-risk situation and exposure reduction/elimination is not possible (3). Disability leave: This option usually is considered by the personal physician for the pregnant women facing reproductive hazards (4). Remove individual from work: This is the last desirable action and is usually reserved for the female worker. For female workers, it is illegal for an employer to terminate an affected woman due to pregnancy. An individual may choose to quit work because of personal reasons, but it is important to help the individual evaluate all the other options and to understand the possible consequences. This option is to be considered only if all the options have been explored and the individual is comfortable with the possible consequences (10).

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TOKSIČNI AGENSI I BOLESTI REPRODUKTIVNOG SISTEMA

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SAŽETAK

Reproduktivni sistem je jedan od najosetljivijih kada je u pitanju dejstvo toksičnih materija. Zato je neophodno usmeriti pažnju ka poznavanju ovog problema i biti na oprezu pri ekspoziciji. Za mnoge agense je poznato da mogu imati štetne posledice na reprodukciju i razvoj jedinke. Posledice dejstva u smislu izmene strukture hromozoma su brojne, moguća je pojava mentalne retardacije, anomalije, neplodnost i malignitet. Povećan broj hromozomskih aberacija zapažen je kod radnika izloženih hemikalijama kao što su benzen, stiren, etilen oksid, epihlorhidrin arsen, hrom i mangan. Toksični agensi mogu ostaviti posledice u smislu poremećaja produkcije sperme direktnim dejstvom i da indirektno remete hormonsku regulaciju spermatogeneze. Seksualna aktivnost može takođe biti poremećena zbog smanjenog libida, inhibirane erekcije i ejakulacije. Ovogeneza kod eksponiranih žena radnica toksičnim agensima može biti poremećena, sa brojnim posledicama. Ekspozicija ovim agensima posle tri meseca trudnoće može da dovede do problema, poremećaja razvoja fetusa, funkcionalnih i nervnih abnormalnosti ploda ali i do povećanog rizika trudnoće sa mogućom eklampsijom i prevremenim porođajem. Lekar medicine rada može sprečiti ili umanjiti pomenute rizike po zdravlje eksponiranih radnika edukacijom, promocijom zdravlja i posredovanjem kod promene radnog mesta ili eliminacije ekspozicije.

Ključne reči: **reproduktivni sistem, radno mesto, toksični agensi**