Horny H-P, Parwaresch MR, Lennert K. Bone marrow findings in systemic mastocytosis. *Hum Pathol* 1985; **16:** 808–14.

Kettelhut BV, Parker RI, Travis WD, et al. Hematopathology of the bone marrow in pediatric cutaneous mastocytosis. *Am J Clin Pathol* 1989; **91:** 558–62.

Lawrence JB, Friedman BS, Travis WD, et al. Hematologic manifestations of systemic mast cell disease: a prospective study of laboratory and morphologic features and their relation to prognosis. *Am J Med* 1991; **91:** 612–24.

Ridell B, Olafsson JH, Roupe G, et al. The bone marrow in urticaria pigmentosa and systemic mastocytosis. *Arch Dermatol* 1986; **122:** 422–27.

Travis WD, Li C-Y. Pathology of the lymph node and spleen in systemic mast cell disease. *Modern Pathol* 1988; **1:** 4–14.

Pathophysiology

Burd PR, Rogers HW, Gordon JR, et al. Interleukin 3-dependent and independent mast cells stimulated with IgE and antigen express multiple cytokines. *J Exp Med* 1989; **170:** 245–57.

Galli SJ. New concepts about the mast cell. *N Engl J Med* 1993; **328:** 257–65.

Galli SJ, Iemura A, Garlick DS, et al. Reversible expansion of primate mast cell populations in vivo by stem cell factor. *J Clin Invest* 1993; **91:** 148–52.

Galli SJ, Tsai M, Wershil BK. The *c-kit* receptor, stem cell factor and mast cells. *Am J Pathol* 1993; **142:** 965–74.

Gordon JR, Burd PR, Galli SJ. Mast cells as a source of multifunctional cytokines. *Immunol Today* 1990; **11:** 458–64.

Graham A, Thody AJ. Mast cell growth factor increases the survival of human melanocytes in culture. *Br J Dermatol* 1996; **134:** 580.

Kirshenbaum AS, Metcalfe DD. The biology and therapy of mastocytosis. In: Galli SJ, Austen KF, eds. Mast cell and basophil differentiation and function in health and disease. New York: Raven Press, 1989.

Nagata H, Worobec AS, Oh CK, et al. Identification of a point mutation in the catalytic domain of the proto-oncogene *c-kit* in peripheral blood mononuclear cells of patients who have mastocytosis with an associated hematological disorder. *Proc Natl Acad Sci USA* 1995; **92:** 10560–64.

Williams DE, Eisenman J, Baird A, et al. Identification of a ligand for the *c-kit* proto-oncogene. *Cell* 1990; **63:** 167–74.

Occupational medicine

Occupational reproductive hazards

Maureen Paul

Although the causes of many reproductive disorders remain unknown, scientific evidence is accumulating to implicate occupational agents in fertility disorders and adverse pregnancy outcomes. Effective assessment and management of workers exposed to reproductive hazards often involves a team-based approach. By identifying potential reproductive hazards, making appropriate referrals, and by educating and advocating for patients, clinicians can play an important part in safeguarding the reproductive health of workers.

Reproductive disorders include a range of adverse outcomes that occur commonly. For example, in the USA about one in seven married couples are involuntarily infertile. Spontaneous abortion occurs in 10–20% of clinically recognised pregnancies. Among liveborn infants, about 7% are of low birthweight and 3% have major malformations. Developmental disabilities are commonly diagnosed during the early years of life.

In attempting to prevent or explain these disorders, patients turn to health-care providers with questions about the effects of workplace exposures on reproductive health. Responding to these inquiries is difficult because of their emotional content, the multifactorial or unknown aetiologies of reproductive problems, and the scarcity of toxicity data on the thousands of chemicals in industrial use. Nonetheless, by educating patients about what is known and by making appropriate interventions, clinicians can have an invaluable role in promoting the reproductive health of workers.

Effects of occupational agents on reproductive system

The complex processes of human reproduction—maturation and transport of the germ cells, fertilisation, implantation, placentation, and development of the conceptus and child—take place under precise hormonal regulation. Toxic agents may disrupt these events, resulting in reproductive dysfunction in men or women or in adverse outcomes of pregnancy.

Effects on fertility

Spermatogenesis is a continuous process of germ-cell division and differentiation, resulting in the production of millions of sperm daily. Occupational agents can affect male fertility by disturbing spermatogenesis directly or by interfering with its hormonal regulation (panel 1).[1,2] In addition, decreased libido and impotence have been reported in workers with heavy-metal poisoning or with occupational exposure to oestrogenic agents, such as oral contraceptives and stilbene derivatives.[3]

Substances that injure male germ cells tend to act at specific phases in their development. The type of cell affected determines both the time required for clinical expression of the injury and the prospects for recovery. For example, the nematocide dibromochloropropane affects stem-cell precursors, which accounts for the long-term or permanent sterility seen in chronically exposed workers.[4] By contrast, ethylene glycol ethers, used as industrial solvents, primarily affect the more mature spermatocytes; since the stem-cell pool is spared, the effects are reversible after exposure ceases.[5]

By contrast with men, women receive a fixed supply of germ cells before they are born. A small number of these cells mature as dominant follicles, and the ova are released periodically throughout the reproductive lifespan. The

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Panel 1: **Selected occupational agents with reported effects on male reproductive function**

Reported effects	Examples
Reduced libido, impotence	Heavy metal poisoning Oestrogenic agents (stilbenes, oral contraceptives)
Hormonal changes	Lead Oestrogenic agents (stilbenes, oral contraceptives, organohalide pesticides)
Spermatotoxicity	Heat Ionising radiation (⩾150 mGy) Lead Inorganic mercury Dibromochloropropane Ethylene dibromide Ethylene glycol ethers Chloropropene Carbon disulphide

remainder undergo natural degradation. Eventually, the germ-cell pool is depleted and the menopause ensues.

Less is known about the effects of workplace exposures on female than on male fertility. Menstrual disorders have been reported among women in various occupations, including athletes and dancers, agricultural workers, and those who make oral-contraceptive pills.[1] Although the mechanisms remain unclear, reduced female fertility has been reported in dental assistants exposed to high levels of nitrous oxide[6] or metallic mercury vapour,[7] in workers in semiconductor manufacture,[8] and in hospital employees with moderate to high physical workloads.[9]

Effects on pregnancy

Although paid employment has a generally beneficial effect on pregnancy outcome,[10] some specific exposures may be risky for pregnant workers. In addition, there is evidence of a role for male-mediated developmental toxicity.[11,12] Potential mechanisms include transmission of deleterious genetic changes to offspring and transfer of toxic agents to the pregnant woman through contact with contaminated semen or workclothes.[13]

Panel 2 lists some physical and chemical agents that may affect pregnancy adversely.[10–24] In addition, biological agents may present a hazard to pregnant women working as carers of young children, and as teachers and health-care providers.[25] For example, rubella virus and cytomegalovirus are well-known teratogens. Prenatal infection with human parvovirus B19, the aetiological agent of fifth disease in school-age children, is associated with non-immune hydrops fetalis and fetal death.

Several studies have found an increased risk of preterm delivery among women whose jobs involve a combination of stressful factors such as standing for long durations, repetitive lifting, and long hours.[10,14] Some research, especially from developing countries, also suggests an association between standing for long durations and low birthweight.[10,15,16]

Studies that assess pregnancy outcome among workers in chemical occupations are difficult to interpret, since most lack information on dose or specific offending agents. However, fairly substantial evidence indicates an increased risk of pregnancy loss among workers exposed to ethylene glycol ethers[22] and among health-care workers exposed to waste anaesthetic gases or antineoplastic agents.[21] In addition, prenatal lead exposure is associated with cognitive deficits in infants, with subtle defects apparent when maternal or cord-blood lead concentrations were as low as 0·48–0·96 µmol/L (10–20 µg/dL).[18]

Clinical assessment

Practitioners may encounter a variety of clinical situations involving potential reproductive hazards, ranging from assessment of the infertile couple to evaluation of workplace risks for patients planning pregnancy or for already pregnant women. Since reproductive disorders have diverse aetiologies, the occupational evaluation is only one part of a broader investigation. Although each case has its unique features, they all involve the following steps.

Identify exposures

The first step is to find out the physical, chemical, and biological agents to which patients may be exposed at work. By taking occupational histories from both the male and the female partner, the clinician can assess the types, routes, and timing of exposure, as well as the potential for secondary contamination of the home environment with toxic agents.

If patients are unsure of the precise identities of chemicals used at work, they may be able to obtain this information from employers. In North America and some European countries, for instance, workers have a legal right to obtain material safety data sheets (MSDS) from employers; these list the hazardous ingredients of chemical products. This information is also available on product labels or from the manufacturers.

Establishment of the timing of exposure is especially important during pregnancy, since the effects of a toxic agent may depend on the stage of gestation at which exposure occurs. For example, high-dose irradiation exposure around the time of implantation can cause death of the conceptus, but sublethal doses are unlikely to be teratogenic because repair processes are effective at this

Panel 2: **Selected occupational exposures with reported effects on pregnancy outcome**

Agent	Reported effects
Physical agents	
Strenous work[10,14–16]	Preterm delivery, low birthweight
Ionising radiation[17]	CNS and growth deficits (high doses); genetic effects/chlldhood leukaemia at doses <50 mGy
Chemical agents	
Lead[18–20]	Neurobehavioural effects, growth deficits
Antineoplastic agents[21]	Spontaneous abortion
Ethylene glycol ethers[5,22] (2-methoxyethanol, 2-ethoxyethanol and acetates)	Spontaneous abortion
Waste anaesthetic gases[21]	Spontaneous abortion
Ethylene oxide[21]	Spontaneous abortion
Methyl mercury[18]	CNS deficits/cerebral palsy with maternal poisoning
Polychlorinated biphenyls[23]	Congenital syndrome with maternal poisoning; possible neurobehavioural and growth deficits at lower doses
Carbon monoxide[24]	Neurological and growth deficits/fetal death with maternal poisoning

stage. During the period of development of the major organs, from the 17th to the 56th day after conception, the embryo is sensitive to teratogenic insult; later exposures can result in growth deficits or functional abnormalities in the offspring.[17]

Once the exposures have been identified, the clinician must find out whether data from human beings or animals suggest reproductive or developmental toxicity. Although the MSDS should provide this information, many have inadequate reproductive-health data or fail to include the data.[26] However, practitioners can obtain reproductive-toxicity data through computer databases such as REPROTOX (telephone +1 202 293 5137) or the Teratogen Information system (TERIS; telephone +1 206 543 2465).

Known reproductive hazards include those for which substantial data from human beings indicate adverse effects at doses commonly found in the workplace. Some developmental hazards affect the fetus only at doses approaching maternal toxicity (eg, methyl mercury), whereas others cause developmental problems at doses that do not necessarily produce overt symptoms in the adult (eg, lead). Suspect hazards include those based on more limited data from human beings or on studies in animals only. Owing to interspecies variations and other factors, clinicians may need to consult experts in toxicology and risk assessment to find out the relevance of data from studies in animals to human beings.

Estimate extent of exposure

The presence of a toxic agent in the workplace is not synonymous with exposure, since absorption into the body must occur for an adverse effect to be produced. Asking patients about measures to control exposure at the workplace may help the clinician to assess the extent of exposure. For instance, some laboratory workers handle chemicals under fume hoods designed to take potentially harmful agents away from the worker's breathing zone. Others work at unventilated benches, where significant exposure to chemicals is more likely.

Commonly, however, exposure assessment requires consultation with occupational-health experts. Industrial-hygiene investigations may be needed to document exposures in the workers' environment and to assess the adequacy of control methods. Consultants may also be useful in interpreting exposure data, since few occupational-exposure limits are designed to protect specifically against reproductive risks.[27]

Biological monitoring of exposure is useful in lead-exposed workers. Blood lead concentrations of about 1·9 µmol/L in men are associated with abnormal semen characteristics; even lower lead concentrations in pregnant women may be a cause for concern. Although assays to measure other chemicals in body fluids are available, the lack of safe reference values for reproductive effects limits their usefulness. Serological testing is indicated for pregnant workers at risk of exposure to harmful viruses. Measurement of virus-specific IgM and IgG helps to differentiate immune women from those who are susceptible or primarily infected, forming a basis for rational management.

Document adverse health effects

Although no physical findings are specifically indicative of work-related reproductive disorders, the physical examination may provide important aetiological clues. For example, gynaecomastia in a male worker suggests exposure to oestrogenic agents; the testicles may be small in a worker exposed to gametotoxins. Dermatitis in a pregnant chemical worker may suggest overexposure to agents that also affect fetal development.

In patients with fertility problems, ovulatory function can be investigated by measurement of basal body temperature, urinary assays to detect the preovulatory luteinising-hormone (LH) surge, midluteal serum progesterone measurements, or endometrial biopsy. Since the process of spermatogenesis takes about 74 days in men, serial semen analyses are necessary to assess potential spermatotoxicity. Measurements of serum gonadotropic-hormone concentrations help to differentiate hypothalamic-pituitary dysfunction from direct germ-cell injury. In hypothalamic-pituitary dysfunction, concentrations of follicle-stimulating hormone (FSH) and LH are low; severe insult to the germ cells, on the other hand, is associated with high FSH concentrations. Sonographic imaging of fetal development is indicated in pregnant women exposed to potential teratogens or to chemicals associated with fetal growth deficits, such as carbon monoxide.

Management of patients

The final step involves assimilation of exposure and health-effects data so that the risk to the patient can be estimated and the extent of intervention necessary to protect the health of workers identified. The mainstays of management of patients include counselling, medical recommendations, and control of exposures at the workplace.

The best time to identify and control exposures that may affect parental health or pregnancy outcome is, obviously, before conception. Reduction of exposure to chemicals is clearly warranted when regulatory limits are exceeded, or for even moderate exposures to agents known or suspected to be developmental hazards. Generally, exposure control at the workplace is the best solution; compensated leave from work or transfers before pregnancy may be difficult to arrange. Blood lead concentrations should be measured in at-risk patients and, if possible, lowered to the normal range before conception. Susceptible workers should also be offered vaccination against rubella virus (at least 3 months before conception) and hepatitis B virus.

The most likely time for patients to seek advice, however, is during pregnancy, and many fear that deleterious exposures have already occurred. In these cases, clinicians should provide the best possible appraisal of risk based on the type, timing, and dose of exposure, clearly conveying any limitations in the data. Even when reassurance is warranted, a clinician must never guarantee a perfect outcome, because of the background frequency and diverse aetiologies of reproductive problems.

It is important to place the risk in perspective. For example, a pregnant woman with low-level lead exposure may fear that her child will be mentally retarded. Although follow-up is advisable, she should be informed that the cognitive deficits associated with low doses of lead are subtle and do not usually persist if postnatal exposure is well controlled.[18–20] The concept of relative risk should also be explained. For instance, for a defect that occurs in 1 per 1000 infants, an exposure that doubled the risk would result in a risk of only 2 per 1000. Such information may substantially affect a woman's decisions about whether to continue the pregnancy and her employment options.

Recommendations to terminate a pregnancy because of workplace exposures are almost never warranted. Rare exceptions might include pregnancies affected by ionising-radiation accidents, involving exposures of more than 0·3 Gy, or long-lasting and severe maternal anoxia from chemical poisoning.

Every effort should be made to keep exposure to hazardous chemicals to a minimum throughout the pregnancy. During the second half of pregnancy, job modifications should be sought for pregnant patients in highly strenuous jobs, particularly if they have other risk factors for preterm delivery or low birthweight. If changes are not feasible, clinicians should at least educate patients about the signs of preterm labour, check the cervix frequently during the third trimester, and follow fetal growth carefully. Temporary transfers should be considered for non-immune pregnant workers with potential occupational exposure to rubella, human parvovirus B19, or varicella.

Patients who have already experienced adverse outcomes require especial compassion and support. Despite their quest for answers, the clinician can rarely say with certainly that the workplace contributed to the adverse outcome. Reduction of suspect exposures may still be warranted in these circumstances. Since toxic effects on spermatogenesis are usually reversible, an improvement in semen characteristics after cessation of exposure supports an occupational aetiology. In addition, women who have had miscarriages or have given birth to infants with developmental abnormalities will be reassured if workplace exposures are investigated and controlled before a future pregnancy occurs.

Clinicians who address work-related reproductive concerns should be familiar with their country's laws that govern the responsibilities of employers to maintain safe workplaces and the rights of workers exposed to potential hazards. When a risk is clearly demonstrated, employers are usually legally obliged to institute control measures or to offer transfer to other employment or leave. Pregnant women should be afforded the same rights to transfer, leave, and benefits as other temporarily work-disabled employees.[28]

When the risk is less certain because toxicity data are inadequate or exposures are at low levels, employers may not be obliged to accommodate workers' requests. In these circumstances, practitioners must counsel patients carefully, exploring their options and making sure that their decisions are as well informed as possible. In addition, by communicating with employers and advocating for patients, clinicians can often negotiate acceptable solutions that protect patients' jobs and health.[29]

References

1 Baranski B. Effects of workplace on fertility and related reproductive outcomes. *Environ Health Perspect* 1993; **101** (suppl 2): 81–90.

2 Lahdetie J. Occupation- and exposure-related studies on human sperm. *J Occup Environ Med* 1995; **37:** 922–30.

3 Whelan EA, Grajewski B, Wild DK, Schnorr TM, Alderfer R. Evaluation of reproductive function among men occupationally exposed to a stilbene derivative: II perceived libido and potency. *Am J Ind Med* 1996; **29:** 59–65.

4 Potashnik G, Porath A. Dibromochloropropane (DBCP): a 17-year reassessment of testicular function and reproductive performance. *J Occup Environ Med* 1995; **37:** 1287–91.

5 National Institute for Occupational Safety and Health. Criteria for a recommended standard: occupational exposure to ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, and their acetates. DHHS (NIOSH) publication no 91–119. Cincinnati: NIOSH, 1991.

6 Rowland AD, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N Engl J Med* 1992; **327:** 993–97.

7 Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. *Occup Environ Med* 1994; **51:** 29–34.

8 Eskenazi B, Gold EB, Samuels SJ, et al. Prospective assessment of fecundability of female semiconductor workers. *Am J Ind Med* 1995; **28:** 817–31.

9 Florack E, Zielhuis GA, Rolland R. The influence of occupational physical activity on the menstrual cycle and fecundability. *Epidemiology* 1994; **5:** 14–18.

10 Marbury MC. Relationship of ergonomic stressors to birthweight and gestational age. *Scand J Work Environ Health* 1992; **18:** 73–83.

11 Savitz DA, Sonnenfeld NL, Olshan AF. Review of epidemiologic studies of paternal occupational exposures and spontaneous abortion. *Am J Ind Med* 1994; **25:** 361–83.

12 Savitz DA, Chen J. Parental occupation and childhood cancer: review of epidemiologic studies. *Environ Health Perspect* 1990; **88:** 325–37.

13 Olshan AF, Mattison DR, eds. Male-mediated developmental toxicity. New York: Plenum Press, 1994.

14 Luke B, Mamelle N, Keith L, et al. The association between occupational factors and preterm birth: a United States nurses' study. *Am J Obstet Gynecol* 1995; **173:** 849–62.

15 Launer LJ, Villar J, Kestler E, DeOnis M. The effect of maternal work on fetal growth and duration of pregnancy: a prospective study. *Br J Obstet Gynaecol* 1990; **97:** 62–76.

16 Fortier I, Marcoux S, Brisson J. Maternal work during pregnancy and the risks of delivering a small-for-gestational-age or preterm infant. *Scand J Work Environ Health* 1995; **21:** 412–18.

17 Brent R, Meistrich M, Paul M. Ionizing and nonionizing radiations. In: Paul M, ed. Occupational and environmental reproductive hazards: a guide for clinicians. Baltimore: Williams & Wilkins, 1993: 165–200.

18 Miller RK, Bellinger D. Metals. In: Paul M, ed. Occupational and environmental reproductive hazards: A guide for clinicians. Baltimore: Williams & Wilkins, 1993: 233–52.

19 Bellinger D, Sloman J, Leviton A, Needleman H, Rabinowitz M, Waternaux C. Low-level lead exposure and children's cognitive function in the preschool years. *Pediatrics* 1991; **87:** 219–27.

20 Deitrich KN, Succop PA, Bornschein RL, et al. Lead exposure and neurobehavioral development in later infancy. *Environ Health Perspect* 1990; **89:** 13–19.

21 Ahlborg Jr G, Hemminki K. Reproductive effects of chemical exposures in health professions. *J Occup Environ Med* 1995; **37:** 957–61.

22 Schenker MB, Gold EB, Beaumont JJ, et al. Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. *Am J Ind Med* 1995; **28:** 639–59.

23 Lione A. Polychlorinated biphenyls and reproduction. *Reprod Toxicol* 1988; **2:** 83–89.

24 Koren G, Sharav T, Pastuszak A, et al. A multicenter, prospective study of fetal outcome following accidental carbon monoxide poisoning in pregnancy. *Reprod Toxicol* 1991; **5:** 397–403.

25 Ekblad U. Biological agents and pregnancy. *J Occup Environ Med* 1995; **37:** 962–65.

26 Paul ME, Kurtz S. Analysis of reproductive health hazard information on material safety data sheets for lead and the ethylene glycol ethers. *Am J Ind Med* 1994; **25:** 403–16.

27 US General Accounting Office. Reproductive and developmental toxicants: regulatory actions provide uncertain protection. Washington, DC: US General Accounting Office, 1991.

28 Clauss CA, Berzon M, Bertin J. Litigating reproductive and developmental health in the aftermath of *UAW v Johnson Controls*. *Environ Health Perspect* 1993; **101** (suppl 2)**:** 205–20.

29 Institute of Medicine. Role of the primary care provider in occupational and environmental medicine. Washington, DC: National Academy Press, 1988: 5.