PART 1
Hazards to Pregnancy

PROTOCOL 1

Developmental Toxicology and Teratology

James W. Hanson

Center for Developmental Biology and Perinatal Medicine, National Institute of Child Health and Human Development, Bethesda, MD, USA

Exposures to potentially hazardous agents during pregnancy are common. Such agents include drugs (both therapeutic agents and abused substances), environmental chemicals, infectious agents, physical agents (radiation, heat and mechanical factors) and maternal health conditions. Many of these exposures are not readily avoidable, as pregnancy is often not planned or recognized for an extended period after conception, or because there is a continuing need for maternal treatment for health conditions (e.g. epilepsy, infection, asthma, chronic cardiovascular disorders). Exposure to various agents in the home or workplace, or as a consequence of maternal lifestyles and self-medication, is almost universal, and pre-conception planning only rarely provides an opportunity to identify exposures of concern. As a consequence, questions about the significance of such an exposure, whether stated or not, are often a source of concern to pregnant women or their care provider.

Not all developmental toxicants need result in permanent adverse outcomes for the fetus or newborn. Some agents may have at least partially reversible or transient effects if recognized early, such as fetal growth restriction from tobacco smoking. It is important to recognize that structural birth defects resulting from exposure to human teratogens are not the only manifestations of exposure to developmental toxicants. Fetal or postnatal growth disorders, functional developmental disorders including cognitive and behavioral deficits, abnormalities of placental function putting the fetus at increased risk, and death (embryonic, fetal, perinatal or postnatal) are all among potential manifestations of exposures. Furthermore, some adverse outcomes may not become apparent until many years later (e.g. reproductive consequences and cancer from exposure to diethylstilbestrol).

Protocols for High-Risk Pregnancies, 5th edition. Edited by J.T. Queenan, J.C. Hobbins and C.Y. Spong.

Pathogenetic factors in evaluation of risk from exposure to teratogens and other developmental toxicants

When evaluating the likely significance of exposure to potentially hazardous agents, it is essential to consider the following issues in the context of the known or likely pathogenetic mechanisms for adverse fetal outcomes.

Dose and duration of exposure

- In general, the larger the dose, the more likely an effect, and the more likely the effect will be significant.
- Likewise, the longer the duration of exposure, the greater the chance that susceptible periods of organogenesis and development will be encountered.

Timing

- Timing of exposure is critical: certain organ systems may have a limited period of susceptibility for damage.
- Although it is commonly thought that damage can only result during the period of organogenesis, i.e. during the first trimester, this is not correct. Some organ systems (e.g. the brain) undergo developmental processes later in pregnancy and can be damaged throughout the prenatal period.

Pathogenetic mechanism(s)

- Teratogens and developmental toxicants produce their adverse effect by specific mechanisms. As these mechanisms are often important in multiple tissues and organs, it is not surprising that several specific types of damage may result.
- Those agents that affect basic morphogenetic processes commonly are related to first trimester exposures. However, those agents which act through mechanical pressures are likely to have the greatest impact during the third trimester, and those agents that produce necrosis through inflammation and/or hemorrhage can potentially destroy normally developing structures throughout pregnancy.

Host susceptibility

- Variability in the genetic factors related to metabolism of drugs and chemicals may result in differential susceptibility of the host. These pharmacogenetic factors must be expressed at a relevant time in the tissue or organ system affected.
- There are two potentially relevant 'hosts' to be considered. Mother and embro/fetus only share 50% of the genome. Thus, depending on the pathogenesis of the adverse outcome, maternal or fetal (or perhaps both) genotype may be more important.

Exposures to human teratogens and developmental toxicants commonly are manifest across a wide spectrum of effects. At the severe end, a clinically recognizable pattern of effects (a 'syndrome') may be identified. However, variability of manifestations within the scope of specific adverse outcomes comprising a syndrome is the rule. Among the population of exposed and affected infants, less severe and less pervasive manifestations are often more frequent. Thus infants exposed to alcohol prenatally may have outcomes ranging from mild effects on cognition and behavior from smaller amounts consumed on a few occasions, to the full-blown fetal alcohol syndrome.

Table 1.1 presents a list of agents, including therapeutic agents, for which substantial human data is available establishing a risk for humans.

Table 1.1 Important human teratogens

Agent	Dose	Susceptible period
Medications		
Acitretin	Usual therapeutic	1st trimester
Aminopterin	Usual therapeutic	1st trimester
Amodarone	Usual therapeutic	12 weeks–term
Androgens (including danazol)	Usual therapeutic	Unknown
Angiotensin II receptor inhibitors (candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, valsartan)	Usual therapeutic	2nd and 3rd trimesters
Angiotensin-converting enzyme inhibitors (benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril)	Usual therapeutic	2nd and 3rd trimesters
Carbamazepine	Usual therapeutic	1st trimester
Clonazepam	Usual therapeutic	1st trimester
Coumarin anticoagulants	Usual therapeutic	1st trimester
Cyclophosphamide	Usual therapeutic	1st trimester
Diethylstilbestrol	1.5–150 mg/d	1st and 2nd trimesters
Ethosuximide	Usual therapeutic	1st trimester
Etretinate	Usual therapeutic	1st trimester
Fluconazole	Chronic, parenteral, 400–800 mg/d	1st trimester
Indomethacin	Usual therapeutic	2nd and 3rd trimesters
Isotretinoin	Usual therapeutic (oral)	1st trimester
Lithium	Usual therapeutic	1st trimester
Methimazole	Usual therapeutic	1st trimester (malformations) 12 weeks–term (hypothyroidism, goitre)
Methotrexate	≥12.5 mg/wk	1st trimester

(*Continued*)

Table 1.1 (Continued)

Agent	Dose	Susceptible period
Methylene blue	Intra-amniotic injection	2nd trimester
Misoprostol	Usual therapeutic	1st and 2nd trimesters
Penicillamine	Usual therapeutic	Unknown
Phenobarbital	Usual therapeutic	1st trimester
Phenytoin	Usual therapeutic	1st trimester
Primidone	Usual therapeutic	1st trimester
Quinine	≥2g/d	Entire pregnancy
Tetracyclines (chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline, tetracycline)	Usual therapeutic	1st trimester
Thalidomide	Usual therapeutic	41–54 days
Trimethadione, paramethadione	Usual therapeutic	1st trimester
Trimethoprim	Usual therapeutic	1st trimester
Valproic acid	Usual therapeutic	1st trimester
Agents of abuse		
Alcohol	Abuse	Unknown
Cigarette smoking	Risks greater with heavy smoking	Entire pregnancy
Cocaine	Abuse	Entire pregnancy
Toluene	Abuse (inhalation)	Unknown
Environmental exposures		
Methyl mercury	Associated with maternal methylmercury concentration ≥0.1 μg/mL	Unknown
PCBs	Toxic exposure	Unknown
Infections		
Varicella	Primary infection (much smaller risk with recurrent infection)	Entire pregnancy (but higher in 2nd trimester)
Parvovirus B19	Primary infection	Entire pregnancy (but higher in 2nd trimester)
Cytomegalovirus	Primary infection (much smaller risk with recurrent infection)	Entire pregnancy (but much higher in first half)
Syphilis	–	2nd and 3rd trimester
HIV	–	3rd trimester, especially during labor
LMCV	–	Unknown
Toxoplasmosis	Primary infection	Entire pregnancy

(*Continued*)

Table 1.1 (Continued)

Agent	Dose	Susceptible period
Rubella	Primary infection (rarely secondary infection)	1st and 2nd trimester (but much higher in 1st trimester)
Maternal illnesses and conditions		
Maternal diabetes mellitus	–	1st trimester
Maternal autoantibodies (Rh, SLE, platelet)	–	2nd and 3rd trimester
Maternal endocrinopathies	–	Unknown
Maternal phenylketonuria	Untreated	Unknown
Maternal obesity	Risk greater with severe obesity than with mild obesity	1st trimester
Physical agents		
Chorionic villus sampling	–	<10 weeks
Early amniocentesis	–	<14 weeks
Ionizing radiation	>10–20 cGy	Entire pregnancy (but highest in 1st trimester)
Radioactive iodine	Therapeutic	12 weeks–term

Table 1.2 Information resources: computerized databases

Database	Contact
REPROTOX	(202) 687-5137
TERIS	(206) 543-2465

The list continues to grow as new research reveals more details about the magnitude and nature of risks associated with many of these and other newly recognized agents. Thus it is important to check the current literature before counseling an exposed family. A variety of information resources, ranging from Internet-based computerized databases and commercially available information resources, to standard reference resources for further reading are listed in Table 1.2.

For the clinician whose practice only rarely encounters these questions, or for those who encounter a question for which current data is limited or difficult to access, consultation with a specialist may be an appropriate option. Many states or academic centers have established Teratogen Information Services to help meet this need. Table 1.3 presents a current listing of these resources.

Table 1.3 Teratogen information services in North America

Service	Telephone number
Alabama Birth Defects Surveillance	(800) 423-8324 or (334) 460-7691
Arizona Teratogen Information Program	(888) 285-3410 or (520) 626-3410 (in Tucson)
Arkansas Teratogen Information Service	(800) 358-7229 or (501) 296-1700
CTIS Pregnancy Risk Information	(800) 532-3749 (CA only)
IMAGE: Info-Medicaments en Allaitement et Grossesse, Province of Quebec, Canada	(514) 345-2333
Motherisk Program, Ontario, Canada	(416) 813-6780
Connecticut Pregnancy Exposure Information Service	(800) 325-5391 (CT only) or (860) 679-8850
Reproductive Toxicology Center, District of Columbia, MD	(301) 620-8690 or (301) 657-5984
Illinois Teratogen Information Service	(800) 252-4847 (IL only) or (312) 981-4354
Indiana Teratogen Information Service	(317) 274-1071
Massachusetts Teratogen Information Service (MaTIS)	(800) 322-5014 (MA only) or (781) 466-8474
Genetics & Teratology Unit, Pediatric Service, Massachusetts General Hospital	(617) 726-1742
Missouri Teratogen Information Service (MOTIS)	(800) 645-6164 or (573) 884-1345
Nebraska Teratogen Project	(402) 559-5071
Pregnancy Healthline, Southern New Jersey Perinatal Cooperative	(888) 722-2903 (NJ) or (856) 665-6000
Pregnancy Risk Network	(800) 724-2454 (then press 1) (NY only) or (716) 882-6791 (then press 1)
PEDECS, Rochester, NY	(716) 275-3638
NCTIS Pregnancy Exposure Riskline	1-800-532-6302 (NC)
North Dakota Teratogen Information Service	(701) 777-4277
Texas Teratogen Information Service	(800) 733-4727 or (940) 565-3892
Pregnancy RiskLine, Salt Lake City, UT	(801) 328-2229 or (800) 822-2229
Pregnancy Risk Information Service	800-531-9800 (VT only) and 800-932-4609
CARE Northwest, Seattle, WA	(888) 616-8484
West Virginia University Hospitals	(304) 293-1572
Wisconsin Teratogen Information Service	(800) 442-6692
Workplace Hazards to Reproductive Health, Madison, WI	(608) 266-2074

For information regarding the Teratology Information Service in your area, contact the Organization of Teratology Information Services (OTIS) at: (866) 626-6847 or http://www.otispregnancy.org.

Suggested readings

Bennett PN. *Drugs and Human Lactation*. Amsterdam: Elsevier, 1988.

Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*, 6th edn. Baltimore: Williams & Wilkins, 2001.

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Paul M: *Occupational and Environmental Reproductive Hazards*. Baltimore: Williams & Wilkins, 1993.

Schardein JL. *Chemically Induced Birth Defects*. 3rd edn. New York: Marcel Dekker, 2001.

Scialli AR. *A Clinical Guide to Reproductive and Developmental Toxicology*. Boca Raton: CRC Press, 1992.

Shepard TH. *Catalog of Teratogenic Agents*, 10th edn. Baltimore: Johns Hopkins, 2001.