

IN SUMMARY  
HUMAN TERATOLOGY

**TERATOLOGY**

**DEFINITION**

An exposure in pregnancy that has a harmful fetal effect.

1. An increase in the frequency of an abnormal fetal effect
2. A dose-response relationship
3. Established mechanism of action, which often requires animal model
4. The proposed teratogenicity must make sense biologically
5. Identifying a genetically more susceptible group.  
Clinical epidemiologic studies  
e.g. features of exposed and controls  
Animal models  
- address issues of dose  
- determine cellular effects

**POTENTIAL FETAL EFFECTS**

Spontaneous abortion	Maternal diabetes
Growth restriction	Alcohol
Pattern of major and minor anomalies	Anticonvulsant drugs, Warfarin, retinoic acid
Major malformations only	Cigarette smoking
Stillbirth	Maternal diabetes
Abruptio placenta	Cocaine
Cognitive dysfunction	Retinoic acid, PCB phenobarbital, lead
Altered social behavior	Diethylstilbestrol (DES)
Cancer	DES

**DISTINCTIVE PHENOTYPIC EFFECTS**

- Nose hypoplasia in Warfarin-exposed
- Ear malformations in retinoic acid (Accutane)-exposed
- Severe nail hypoplasia and fused interphalangeal joints in phenytoin-exposed
- Vascular disruption defects in CVS-exposed and misoprostol-exposed

**PERIOD OF GREATEST SENSITIVITY**

KNOWN FOR VERY FEW HUMAN TERATOGENS

ex: THALIDOMIDE: days 20-34 post fertilization

WARFARIN: weeks 4-7 post fertilization (anticoagulant)

**DOSE RESPONSE RELATIONSHIPS**

- VALPROIC ACID
- MATERNAL PHENYLKETONURIA (PKU)
- ALCOHOL
- CIGARETTE SMOKING

**MUST MAKE SENSE BIOLOGICALLY**

Ex. EXOGENOUS SEX HORMONES

- NOT PLAUSIBLE BECAUSE FETAL TISSUES ALLEGEDLY AFFECTED (HEART, LIMBS) HAVE NO RECEPTORS FOR HORMONES



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HST 071

**SPINA BIFIDA**

**DEFINITION:** Defect in closure of neural tube in lumbar  
or thoracic region  
**PREVALENCE:** 0.4 per 1,000 U.S. Caucasians  
0.4 per 1,000 African-Americans  
0.6 per 1,000 Hispanics  
**ETIOLOGY:** Combined effect of genetic and non-  
genetic factors

**CANDIDATE GENES:** methylenetetrahydrofolate  
reductase (MTHFR) [C677T]; methionine  
synthase, sonic hedgehog, uncoupling protein 2

**ENVIRONMENTAL FACTORS:** Folic acid deficiency,  
maternal diabetes mellitus, maternal obesity,  
anticonvulsant drugs (Tegretol and Depakote)

**MOST EXPOSURES HAVE NOT BEEN STUDIED**

- ◆ MOST STUDIES FOCUS ON MAJOR MALFORMATIONS ONLY
- ◆ LITTLE DATA ON EFFECTS ON BEHAVIOR AND I.Q.
- ◆ FEW STUDIES OF DERMAL EXPOSURES  
AIRBORNE EXPOSURES
- ◆ NEED TO ESTABLISH MOLECULAR BASIS FOR TERATOGENESIS

COUNSELING FOR EXPOSURES: IT IS NOT GENETIC COUNSELING

**MICROTIA**

**DEFINITION:** MALFORMED AND UNDERDEVELOPED EAR;  
MILD TO SEVERE; USUALLY UNILATERAL  
RIGHT > LEFT  
**ASSOCIATIONS:** TYPICALLY ISOLATED;  
NO INCREASE IN KIDNEY ABNORMALITIES  
HEARING LOSS: 50 TO 70dB  
**PREVALENCE:** 1 IN 10,000  
**GENETICS:** 7% EMPIRIC RECURRENCE RISK

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Friedman, J.M., and Janine E. Polifka. *Teratogenic Effects of Drugs: A Resource for Clinicians: TERIS*.  
Baltimore, MD: Johns Hopkins University Press, 1994. ISBN: 0801848008.

**ACUTANE**

35% Have Major Malformations

- Conotruncal Heart Defects
- Cranial Nerve Palsies
- Absence of Vermis of Cerebellum
- Moderate to Severe Mental Retardation

25% Of Children With No Malformations Are Mentally Retarded

**PHYSICIAN'S DESK REFERENCE (PDR)**

SECTION ON RISKS IN PREGNANCY DESIGNED TO PROTECT LIABILITY

TWO SYSTEMATIC STUDIES SHOWED POOR CORRELATION BETWEEN CATEGORIES A, B, C, D AND X WITH CLINICAL DATA AVAILABLE

STUDY OF ALL DRUGS APPROVED BY FDA 1980-2000  
468 DRUGS: 80% "RISK UNDETERMINED"  
USED ONLINE "TERIS" AS SOURCE

POOR CORRELATION OF TERIS RATINGS AND FDA DRUG  
CATEGORIES (A, B, C, D & X) FOR 163 DRUGS  
KAPPA STATISTIC =  $0.08 \pm 0.04$

**OTIS**

Example: Centers collaborate to identify exposed pregnancies and organize follow-up exams.

Examples: asthma medication  
leflunomide (Arava)

Outcomes: body and head size, dysmorphic features, major malformations

**TERATOGEN COUNSELING VS GENETIC COUNSELING**

ALIKE: PREPARATION FOR MEETING  
COMMUNICATION  
RISK ASSESSMENT  
SPERM OR EGG DONOR

DIFFERENT: PERIOD OF EXPOSURE  
ALTERNATIVE TREATMENTS  
EGG DONOR  
PRENATAL DIAGNOSIS LIMITED  
PREVENTION: AVOIDANCE

**RECOGNIZED HUMAN TERATOGENS (2004)**

1. DRUGS

Aminopterin/amethopterin  
Androgenic hormones  
Angiotensin converting  
enzyme(ACE) inhibitors  
Busulfan  
Carbamazepine  
Chlorobiphenyls  
Cocaine  
Cyclophosphamide  
Cyclosporin  
Diethylstilbestrol  
Etretinate  
Fluconazole  
Heroin/methadone  
Iodide  
Isotretinoin (13-cis-retinoic  
acid)  
Lithium  
Methimazole  
Phenobarbital  
Phenytoin  
Propylthiouracil  
Prostaglandin  
Tetracycline  
Thalidomide  
Trimethadione/paramethadione  
Valproic acid  
Warfarin

2. HEAVY METALS

Lead

Mercury

3. RADIATION

Cancer therapy

4. MATERNAL CONDITIONS

Alcohol  
Insulin-dependent diabetes  
mellitus  
Iodide deficiency  
Maternal phenylketonuria  
Myasthenia gravis  
Obesity, severe  
Smoking cigarettes/marijuana  
Systemic lupus erythematosus  
Vitamin A deficiency

5. INTRAUTERINE INFECTIONS

Cytomegalovirus  
Herpes simplex

Parvovirus  
Rubella  
Syphilis  
Toxoplasmosis  
Varicella  
Venezuelan equine encephalitis  
Virus

6. OTHER EXPOSURES

Chorionic Villus Sampling (CVS)  
Dilation and Curettage (D & C)  
Gasoline fumes (excessive)  
Heat  
Hypoxia  
Intracytoplasmic Sperm  
Injection (ICSI)  
Methyl isocyanate  
Methylene blue  
Polychlorinated biphenyls  
Toluene (excessive; glue  
sniffing)  
Trauma, blunt

FUNDAMENTAL QUESTIONS
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1. What is a teratogen?
2. Describe the embryologic time line for teratogenesis?
3. What are the specific abnormalities that are seen in the fetal Warfarin syndrome?
4. What are the specific abnormalities that are seen the fetal alcohol syndrome?
5. What are the specific abnormalities that are seen in the fetal hydantoin syndrome?
6. List 10 known anatomic teratogenic fetal effects of drugs?
7. Name 7 infectious diseases known to be teratogenic? In what trimester are these of greatest concern?
8. Name 7 mechanical causes of teratogenic effects?
9. What are the adverse fetal effects of prenatal cigarette exposure?
10. What are the effects of fetal exposure to Accutane? How may these be prevented?
11. What is a good reference source to use in counseling patients about teratogenic effects of drugs?

