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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- FDA REMOVED WARNING FROM PACKAGE INSERT

Ex. BENDECTIN (VITAMIN B6 AND ANTIHISTAMINE)
- SCIENTIFIC EVIDENCE LACKING
- DRUG RE-INTRODUCED IN CANADA

GENETICALLY MORE SUSCEPTIBLE GROUPS
1. CIGARETTE SMOKING
2. ALCOHOL
3. FOLIC ACID DEFICIENCY

\[
\text{Ethanol} \rightarrow \text{Acetaldehyde} \rightarrow \text{Acetate}
\]

Enzyme: \( \text{Alcohol Dehydrogenase} \) \( \text{Aldehyde Dehydrogenase} \)

Gene loci: ADH1, ADH2, ADH3, ADH4 \( \text{ALDH2} \)

Polymorphisms:
- \( \text{ADH2}^1 \)
- \( \text{ADH2}^2 \) (high Km, high Vmax)
- \( \text{ADH2}^3 \) (high Km, high Vmax)
- \( \text{ADH3}^1 \)
- \( \text{ADH3}^2 \)
- \( \text{ALDH2}^1 \) (active)
- \( \text{ALDH2}^2 \) (inactive)
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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
♦ 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 RECURRENT RISK

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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 ± 0.04

OTIS
Example: Centers collaborate to identify exposed pregnancies and organize follow-up exams.
Examples: asthma medication lleflunomide (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
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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
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?