Teratogens

Teratogen: Definition

- Environmental factor(s) which can adversely affect the developing embryo

1. Key Concepts

- Certain stages are critical
  - Timing of exposure
- Threshold phenomenon
  - Not every exposure is affected
- Variable expression is the rule
- Rarely produce single anomalies
  - Patterns of anomalies
- Anomalies are not specific
2. Variables Affecting the Teratogenic Potential of an Agent

- Nature of the agent
- Timing of the exposure
- Pattern of exposure
- Fetal susceptibility

Nature of the Agent

- Ability to cross the placenta
  - Molecular size / weight
  - Charge
  - Lipophilic / lipophobic
- Mechanism of action
  - vasoconstrictor / vasodilator
  - alters DNA
  - changes rate of cell growth
  - modulates apoptosis

Timing of the Exposure

- Early first trimester - miscarriage
- First trimester - malformations (high degree of sensitivity days 18 - 60)
- Second / third trimester - pregnancy viability, CNS malformations / maturation, fetal growth
- Perinatal - neonatal adaptation
Pattern of Exposure

- Dosage
- Duration
- Continuous versus intermittent

Fetal Genetic Susceptibility to Teratogenesis

Why are only some babies born with FAS?

- Not differences in types of alcohol
- Amount of alcohol
- Drinking pattern
- Maternal genetic factors
- Fetal genetic factors
- Co-teratogens
  - nutrition
Paternal Exposures

- No convincing data exists to document any paternal exposures can be teratogenic
- Irradiation to paternal gonads may induce chromosome breakage

3. Major Teratogens

- Alcohol
- Cigarettes
- Medications
- Ionizing radiation
- Chemicals / occupational exposures
- Over the counter preparations, vitamins
- Illicit drugs
- Hormones
- Infectious
- Maternal health status

Cigarettes

- Association with low birth weight
- Increased incidence of oro-facial clefting
Important Medications
- Isotretinoin
- Anticonvulsants
- Antidepressants
- Chemotherapy
- Lithium

Ionizing Radiation
- X-rays / diagnostic studies
- Electromagnetic radiation
  - No evidence that computer monitors, power lines, etc. are problematic

Occupational Exposures
- Chemicals
- Radiation
Over the Counter Meds
Homeopathic Therapies

- Just because something is ‘natural’ doesn’t mean it is safe.
- Curare is natural

Substances of Abuse

- Amphetamines
- Marijuana
- Cocaine
- Heroin
- Inhalants

- Most are ‘poly-users’

Hormones
**Infectious**
- TORCH infections
- Lymphocytic choriomeningitis virus (LCMV)

**Maternal Health Issues**
- Diabetes
- PKU
- Lupus
- Nutrition
- Hyperthermia

**Maternal Health**
- Nutritional status
  - general
  - folic acid
  - zinc
- Medical conditions
  - diabetes
  - infectious agents
- Exercise / fitness
Maternal Diabetes

- Perinatal issues
  - Hypoglycemia, hypocalcemia, hypomagnesemia, polycythemia
  - LGA
- Birth defects 2–3X more common with good control
  - Incidence increases with poorer control

Folic Acid and Neural Tube Defects

- Studies on NTD's in the early eighties culminated with a double-blind, randomized trial done by the MRC Vitamin Group in Great Britain. This trial showed that 4mg/day of folic acid given periconceptionally decreased recurrence by 72% in high risk families
- Probably 50% of all NTD's are preventable by the pre-conceptional use of folic acid.

Folic Acid

- Neural Tube Defects
- Cleft Lip and Palate
- Congenital Heart Disease
- Obstructive uropathies
- Pyloric stenosis
- Limb reduction defects
Folic Acid Supplementation in the Prevention of NTD’s

<table>
<thead>
<tr>
<th>General Population</th>
<th>Increased risk</th>
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<tbody>
<tr>
<td></td>
<td>0.4 - 0.8 mg/day</td>
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<tr>
<td>1. Previous pregnancy with NTD</td>
<td>4 mg/day</td>
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<tr>
<td>2. Close relative with NTD</td>
<td>4 mg/day</td>
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<tr>
<td>3. Women with epilepsy on valproate or carbamazepine</td>
<td>1-2 mg/day</td>
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<tr>
<td>4. Women with IDDM</td>
<td>4 mg/day</td>
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The Role of Vitamins and Cofactors in Teratogenesis

- Diet
  - Diabetes Mellitus
  - Hyperinsulinemia
  - Protein glycosylation
- Ketone bodies
- Anti-epileptic Drugs
- Homocysteine
- Folate
- Zine
- Iron
- Ethanol
- Decreased rate of cellular growth
- (?)

4. Strategies to Reduce Risk
   - Preconception counseling
     - Stabilize weight
     - CMV and rubella titers
     - Discontinue tobacco and alcohol
   - Vitamin supplementation (prior to conception)
   - Evaluate risks / benefits of any medication
   - Minimize first trimester exposures
   - If possible avoid poly-drug use