HUMAN TERATOGENS: UPDATE 2010
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The author of this research has no financial or other interests which post a conflict of interest.
**DEFINITION OF A TERATOGEN**

An exposure in pregnancy that has a harmful fetal effect.

**RECOGNIZED HUMAN TERATOGENS**

1. **DRUGS:**  
   Ex. anticonvulsants  
   methimazole  
   retinoic acid (Accutane)  
   warfarin

2. **HEAVY METALS:**  
   Ex. lead  
   mercury

3. **RADIATION:** cancer therapy; not diagnostic X-rays

4. **MATERNAL CONDITIONS**  
   Ex. insulin-dependent diabetes, cigarette, smoking, alcohol abuse

5. **INTRAUTERINE INFECTIONS**  
   Ex. toxoplasmosis  
   rubella  
   varicella

6. **PROCEDURES**  
   Ex. CVS  
   D & C  
   ICSI  
   amniocentesis

7. **OTHER**  
   Ex. hypotension  
   misoprostol  
   heat
HUMAN TERATOGENS UPDATE - 2010

1. CHARACTERISTICS OF A HUMAN TERATOGEN

2. INFORMATION SOURCES

3. MAJOR LIMITATIONS IN KNOWLEDGE

4. DIFFICULTIES IN COUNSELING

CHARACTERISTICS OF A HUMAN TERATOGEN

1. An increase in the frequency of an abnormal fetal effect;
2. A dose-response relationship; there is a threshold below which the exposure is not teratogenic;
3. Period of greatest sensitivity;
4. Established mechanism of action, which often requires animal model;
5. The proposed teratogenicity must make sense biologically;
6. Identifying a genetically more susceptible group.
<table>
<thead>
<tr>
<th>POTENTIAL FETAL EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion</td>
</tr>
<tr>
<td>Growth restriction</td>
</tr>
<tr>
<td>Pattern of major and minor anomalies</td>
</tr>
<tr>
<td>Major malformations only</td>
</tr>
<tr>
<td>Stillbirth</td>
</tr>
<tr>
<td>Abruptio placenta</td>
</tr>
<tr>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td>Altered social behavior</td>
</tr>
<tr>
<td>Cancer</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
EPIDEMIOLOGIC STUDIES: CASE-CONTROL

EX. Sodium valproate-exposed pregnancies showed increased risk of spina bifida:

Odds Ratio: 20.6 (p < 0.000001)


PROBLEM: A case-control study focuses on only selected effects; does not describe the spectrum of fetal effects.
EPIDEMIOLOGIC STUDIES: COHORT STUDY

EX: Anticonvulsant drugs

Exposed and unexposed infants examined systematically to determine the spectrum of physical effects

- Midface and Digit Hypoplasia
- Major malformations
- Microcephaly
- Growth restriction


THE THRESHOLD DOSE CONCEPT

-- there is for some teratogens a level of exposure below which there is no harmful fetal effect.

Brent RL: Teratology 34:359-360, 1986

Table 1. Teratogenic effects and their frequencies relative to the degree of maternal hyperphenylalaninemia in offspring from untreated maternal phenylketonuria and hyperphenylalaninemia

<table>
<thead>
<tr>
<th>Offspring Abnormality</th>
<th>Maternal Phenylalanine (μM)^a</th>
<th>&gt;1200</th>
<th>1000-1200</th>
<th>600-1000</th>
<th>200-600</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental Retardation</td>
<td>92%</td>
<td>73%</td>
<td>22%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Microcephaly</td>
<td>73%</td>
<td>68%</td>
<td>35%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>12%</td>
<td>15%</td>
<td>6%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>40%</td>
<td>52%</td>
<td>56%</td>
<td>13%</td>
<td></td>
</tr>
</tbody>
</table>

(from Lenke and Levy, '80)

^aTo convert to milligrams per deciliter (mg/dl), multiply by 0.0165

DOSE-RESPONSE RELATIONSHIP

Valproic acid: Omtzigt JGL et al: Neurol 42 (Suppl 5):119,92

Infants with Exposed, spindle bifida but normal

<table>
<thead>
<tr>
<th>(n=5)</th>
<th>(n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA conc. mg/l</td>
<td>VPA conc. mg/l</td>
</tr>
<tr>
<td>73.4 ± 25</td>
<td>43.9 ± 21.6</td>
</tr>
<tr>
<td>Peak dose admin.</td>
<td>Peak dose admin.</td>
</tr>
<tr>
<td>650 ± 124</td>
<td>384 ± 19</td>
</tr>
</tbody>
</table>

Also, see Mawer G et al: Seizure 11:512-18, 2002
## CIGARETTES (mg nicotine/day)

<table>
<thead>
<tr>
<th></th>
<th>NONE</th>
<th>Light &gt;0 to &lt;16</th>
<th>Heavy ≥16</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>64</td>
<td>45</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Mother’s current Smoking (cig/d)</td>
<td>0.4</td>
<td>8.1</td>
<td>16.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Family income (x$1,000)</td>
<td>57.2</td>
<td>58.0</td>
<td>45.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Child’s age (yrs)</td>
<td>14.6</td>
<td>14.5</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>General IQ</td>
<td>115 ± 14.3</td>
<td>109.1 ± 12.4</td>
<td>103.2 ± 11.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Reading</td>
<td>114.</td>
<td>110.</td>
<td>107.</td>
<td>0.01</td>
</tr>
<tr>
<td>Spelling</td>
<td>107.</td>
<td>104.</td>
<td>102.</td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>102</td>
<td>98.</td>
<td>94.</td>
<td>0.05</td>
</tr>
</tbody>
</table>


## DOSE-RESPONSE RELATIONSHIP

### EXAMPLE: ACCUTANE vs. RETIN-A

ACCUTANE, taken by mouth, increases fetal level of all-trans-retinoic acid; 35% rate of major malformations and high rate of mental retardation without malformations.

RETIN-A, applied topically, has little absorbed and is not teratogenic, i.e. no harmful fetal effect.
ACCUTANE
(ISOTRETINOIN; 13-CIS-RETINOIC ACID)

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
TRETINOIN: TOPICAL EXPOSURE IN PREGNANCY  
(all trans retinoic acid)

CLINICAL STUDIES:

Exposed vs. controls showed no increased rate of malformations.

REFERENCES:
Johnson K et al: Teratology 49:375, 1994
TRETINOIN CREAM: PHARMACOKINETIC MODEL

“Topical application of tretinoin in human beings . . . . Results in an internal exposure that is four to six orders of magnitude lower than a minimally teratogenic dose . . . .”


PERIOD OF GREATEST SENSITIVITY:

KNOWN FOR FEW HUMAN TERATOGENS

Ex. THALIDOMIDE: days 20-34 postfertilization
WARFARIN: weeks 4-7
(anticoagulant)
METHOTREXATE: weeks 6-8
(chemotherapy)

IN GENERAL:

1st trimester: malformations
2nd, 3rd trimester: IQ effect
PROPOSED TERATOGENICITY MUST MAKE SENSE BIOLOGICALLY: ONE THAT DID NOT

Example:
BENDECTIN (VITAMIN B6 AND ANTIHISTAMINE)

• SCIENTIFIC EVIDENCE LACKING

• DRUG RE-INTRODUCED IN CANADA

_Brent RL: Reprod Toxicol 13:245-253, 1999._

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_CYP1A1_ MspI polymorphism:

Genotypes:  
AA homozygous wild type  
Aa heterozygous variant type  
aa homozygous variant type

Phase I enzyme: metabolism of chemicals in cigarette smoke

GSTT1 gene, a major phase 2 enzyme:

_Glutathione-S-transferase: GST_  
Genotypes:  
AA: present  
Aa: present  
aa: deletion
### Cigarette smoking, birth weight, mother's genotype: CYP1A1 and GST

<table>
<thead>
<tr>
<th></th>
<th>Smoking</th>
<th>Black</th>
<th>p</th>
<th>White</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL</strong></td>
<td>never</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>continuous</td>
<td>-264 gms</td>
<td>.05</td>
<td>-309 gms</td>
<td>.06</td>
</tr>
<tr>
<td><strong>MOTHER’S GENOTYPE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. CYP1A1</td>
<td>never</td>
<td>+24</td>
<td>.81</td>
<td>+63</td>
<td>.79</td>
</tr>
<tr>
<td></td>
<td>Aa/aa</td>
<td>continuous</td>
<td>-475</td>
<td>.007</td>
<td>-467</td>
</tr>
<tr>
<td>(MSP1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. GSTTI</td>
<td>present</td>
<td>continuous</td>
<td>-61</td>
<td>.70</td>
<td>-291</td>
</tr>
<tr>
<td></td>
<td>absent (deletion)</td>
<td>&quot;</td>
<td>-594</td>
<td>.006</td>
<td>-579</td>
</tr>
</tbody>
</table>


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### Human Teratogens: Information Sources

- Literature searches
  - ACOG Technical Bulletins
- Symposia
- Postgraduate courses
- Annual Meetings
  - Teratology Society
  - DW Smith Workshop
  - Soc Perinatal Epidem
- Books
- Computer – based databases
  - TERIS, Reprotox, Shepard’s Catalog
- OTIS and ENTIS
OTIS - Organization of Teratogen Information Systems

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

http://www.otispregnancy.org/

HUMAN TERATOGENS: LIMITATIONS

• LACK OF KNOWLEDGE
  - MOLECULAR BASIS
  - CELLULAR BASIS
  - EPIGENETIC EFFECTS

• NEED SYSTEMATIC STUDIES OF EFFECTS ON LEARNING AND I.Q.

• NEED STUDIES OF AIRBORNE AND DERMAL EXPOSURES
HUMAN TERATOGENS: MECHANISMS OF ACTION

WARFARIN*: INHIBITION OF VITAMIN K REDUCTASE

PROPYLTHIOURACIL**: BLOCKS CONVERSION OF THYROXINE TO TRIIODOTHYRONINE


HUMAN TERATOGENS: CELLULAR EFFECTS

WARFARIN: Why is nose cartilage affected so dramatically?

VALPROATE: Why does the effect on neural tube produce myelomeningocele and not anencephaly?

PHENYTOIN: Why are effects primarily on distal phalanges of fingers, but not in the toes?
HUMAN TERATOGENS: EPIGENETIC EFFECTS?

One example is assisted reproductive technology (ART): 25% of infants with Angelman Syndrome* had imprinting defect with silencing of maternal UBE3A gene.


ANTICONVULSANTS: EFFECTS ON INTELLIGENCE

ISSUES: AGE OF CHILD
TESTING INSTRUMENT
TESTING PARENTS
SELECTION OF MATCHED CONTROL
EFFECT OF CONFOUNDERS, e.g. SES
<table>
<thead>
<tr>
<th>Domain</th>
<th>PB Effect</th>
<th>Significant p value (1-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Knowledge</td>
<td>Yes</td>
<td>0.035</td>
</tr>
<tr>
<td>Verbal Memory</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Perceptual Organization</td>
<td>Yes</td>
<td>0.054</td>
</tr>
<tr>
<td>Visual Memory</td>
<td>Yes</td>
<td>0.023</td>
</tr>
<tr>
<td>Distractibility</td>
<td>Yes</td>
<td>0.005</td>
</tr>
<tr>
<td>Drawing Ability</td>
<td>Yes</td>
<td>0.035</td>
</tr>
<tr>
<td>Motor Speed</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

* Multivariate ANOVAs were performed using SPSS 11.1

**HUMAN TERATOGENS: COUNSELING ISSUES**

- **MISINFORMATION:** Plague of PDR

- **INCONCLUSIVE STUDIES: EXAMPLES**
  - Selective Serotonin Re-uptake Inhibitors (SSRI)
  - Phthalates
  - Bisphenol A
  - Tumor necrosis factor-alpha antagonist

- **FDA’s ADVERSE EVENT REPORTS: HAVE NOT HELPED TO IDENTIFY HUMAN TERATOGENS**

- **EFFECTS OF LITIGATION**

- **HORNS OF A DILEMMA**
PHYSICIANS 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.

SEE:
- Lo WY, Friedman JM: Ob Gyn 100:465-473, 2002
- Public Affairs Comm (Teratology Society):
- Kweder S: Teratology 63:270, 2001
MOST MEDICATIONS NOT STUDIED FOR FETAL EFFECTS

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


SSRIs

• Celexa (citalopram)
• Lexapro (escitalopram)
• Luvox (fluvoxamine)
• Paxil (paroxetine)
• Prozac (fluoxetine)
• Zoloft (sertraline)
PAROXETINE HYDROCHLORIDE IS A SELECTIVE SEROTONIN-REUPTAKE INHIBITOR AND AN ANTIDEPRESSANT. METABOLIZED BY THE CYTOCHROME P-450 (CYP) 2D6 ISOENZYME. COMPLETELY ABSORBED FROM GI TRACT. ELIMINATION HALF-LIFE 21-24 HOURS.

SSRIs: ? FETAL EFFECTS

GSK Retrospective Study by Ingenix (ctr.gsk.co.uk/welcome.asp)
Finding: Possible “signal” for heart defects, esp. ventricular septal defects, in spontaneous reports in GSK Bupropion Pregnancy Registry.

<table>
<thead>
<tr>
<th>Defect</th>
<th>Bupropion - first trimester (n = 463)</th>
<th>Other antidepressants* first trimester (n = 3,241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>atrial septal defect (ASD)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>coarctation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>tetralogy of Fallot</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>transposition of great arteries</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ventricular septal defect (VSD)</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>total (all defects)**</td>
<td>9</td>
<td>36</td>
</tr>
</tbody>
</table>

* fluoxetine, paroxetine, sertraline, citalopram
** not all specific defects listed
SSRIs AND HEART DEFECTS


<table>
<thead>
<tr>
<th></th>
<th>Paroxetine</th>
<th>Fluoxetine</th>
<th>Sertraline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any heart defect</td>
<td>OR 1.4</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>(0.2, 2.5)</td>
<td>(0.6, 1.5)</td>
<td>(0.9, 2.5)</td>
</tr>
<tr>
<td>Septal defects</td>
<td>0.8</td>
<td>1.2</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(0.3, 2.2)</td>
<td>(0.5, 2.2)</td>
<td>(1.2, 4.0)</td>
</tr>
<tr>
<td>RVOTD</td>
<td>3.3</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>(1.3, 8.8)</td>
<td>(0.2, 3.4)</td>
<td>(0.6, 6.8)</td>
</tr>
</tbody>
</table>

No association with anencephaly, omphalocele or craniosynostosis

SSRIs AND HEART DEFECTS

CDC: National Birth Defects Prevention Study:

All heart defects, all SSRIs – no association
Paroxetine
RVOTO: OR 2.5
(1.0, 6.0)
positive association with anencephaly, omphalocele craniosynostosis
SSRI: Questions about fetal effects

Evidence of dose-response relationships?

Any relevant animal model?

Biologic plausibility

ANY DRUG – SPECIFIC EFFECTS?

Any pattern of dysmorphic features or multiple anomalies?

Any evidence of over-representation of muscular VSDs or tiny ASDs?

HORMONALLY ACTIVE AGENTS: PHTHALATES

“PLASTICIZERS”: PRENATAL EXPOSURE CORRELATES WITH GENITAL EFFECTS IN MALES – TESTIS FUNCTION AND ANOGENITAL DISTANCE


Measuring Anogenital Distance

TUMOR NECROSIS FACTOR ANTAGONIST (TNF-α): ? NEW TERATOGEN

1. Analysis of Adverse Event Reports at FDA: NOT HELPFUL
   Carter JD et al: J Rheumatol 36:635-641, 2009

2. OTIS Findings promising ? Major teratogen
FDA: ADVERSE EVENT REPORTS

USE TO IDENTIFY HUMAN TERATOGENS

FALSE ALARMS:
- TOPICAL TRETINOIN → HOLOPROSENCEPHALY
  FRANZ ROSA

- STATINS →

Selected MMF-Exposed Cases

Le Ray et al., 2004

Tjeertes et al., 2007

Perez-Aytes et al. 2008

Velinov and Zellers, 2008.
PREGNANCY REGISTRIES:

COMPANY BASED:
- Antiretroviral Drugs in Pregnancy Registry:
- VARVAX Pregnancy Registry
- Lamotrigine Pregnancy Registry

HOSPITAL-BASED:
- Isotretinoin Pregnancy Registry
- National Transplant in Pregnancy Registry
- North American AED (antiepileptic drug) Pregnancy Registry

NEED: NATIONAL CENTER TO ADVISE

TERATOGEN COUNSELING: VALPROATE

Patient: 12 weeks GA, taking 1,500 mg/day

Issues: Misinformation ("It's just spina bifida. Take your folic acid and don't worry.")

Risk for developmental delay: hard to quantify
Risk for autism: unknown rate
Prenatal screening: not much help
Change medication: ?
“NEW” TERATOGEN?

SULFONAMIDE: ASSOCIATIONS

ANENCEPHALY : OR 3.4 (95 CI : 1.3 – 8.8)
HLHS : OR 3.2 (95 CI : 1.3 – 7.6)
COARCTATION OF AORTA : OR 3.2 (95 CI : 1.3 – 5.6)

NITROFURANTOIN: ASSOCIATIONS

ANOPHTHALMIA/MICRO- : OR 3.7 (95 CI : 1.1 – 12.2)
HLHS : OR 4.2 (95 CI : 1.9 – 9.1)
CLEFT LIP/PALATE : OR 2.1 (95 CI : 1.2 – 3.9)

METHOD: NBDPS – 13,155 MALFORMED; 4,941 CONTROLS


T.V. ADVERTISEMENT – BOSTON, 2007

ATTORNEY MARK_________
If you took Paxil while pregnant and had a child with a heart defect or pulmonary hypertension, call Attorney Mark ________ at 617-___-_____.

26
TERATOLOGY SOCIETY CHALLENGE

EDUCATE, EDUCATE, EDUCATE

Opportunities at annual meetings
  ? Updates on specific exposures
  ? Annual symposium

Send your students to Human Teratogens Course in Boston

ADVERTISEMENT:
Human Teratogens Postgraduate Course

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Massachusetts General Hospital

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     $325   Nurses, nurse midwives, genetic counselors
     Special arrangements available for students

To Register: Harvard Med-CME
http://cme.med.harvard.edu/courses/humanteratogens

For Information call: Rosanna Greco (Course Coordinator)
Tel: 617-726-1742 or E-mail: Rgreco@partners.org
THE CHALLENGE

“The problem with communication … is the illusion that it has been accomplished.”

George Bernard Shaw