HUMAN TERATOGENS: UPDATE 2010

Lewis B. Holmes, M.D.

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LEWIS B. HOLMES, M.D.

Genetics Unit

MassGeneral Hospital *for* Children

Department of Pediatrics, Harvard Medical School

E-mail: holmes.lewis@mgh.harvard.edu

Tel: 617-726-1742; Fax: 617-724-1911

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

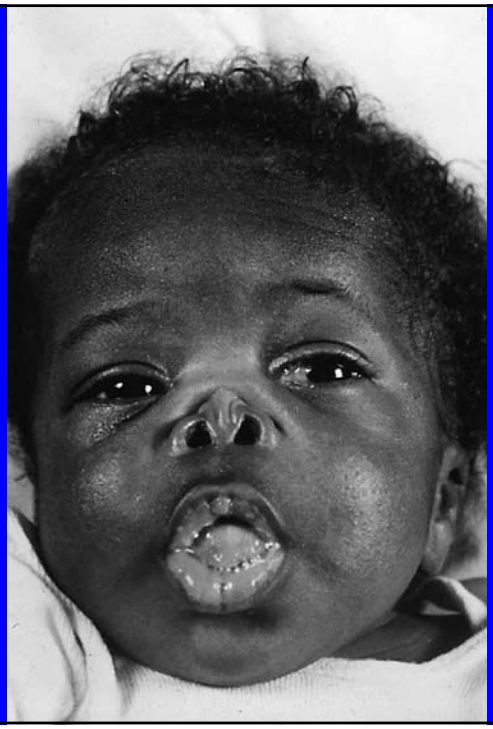
1. CHARACTERISTICS OF A HUMAN TERATOGEN
2. INFORMATION SOURCES
3. MAJOR LIMITATIONS IN KNOWLEDGE
4. DIFFICULTIES IN COUNSELING

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.

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



EPIDEMIOLOGIC STUDIES: CASE-CONTROL

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

Odds Ratio: 20.6 ($p < 0.000001$)

Ref: Robert E, Guibaud P: Lancet 2:937 and 1096, 1982.

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**

Ref: Holmes LB et al: N Engl J Med 344:1132-8, 2001

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

Gaylor DW et al: Teratology 38:389-391, 1988

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

Offspring Abnormality	Maternal Phenylalanine (μM)[a]			
	>1200	1000-1200	600-1000	200-600
Mental Retardation	92%	73%	22%	21%
Microcephaly	73%	68%	35%	24%
Congenital heart disease	12%	15%	6%	0
Low birth weight	40%	52%	56%	13%

(from Lenke and Levy, '80)

[a]To 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 spina bifida (n=5)	Exposed, but normal (n=84)	
VPA conc. mg/l	73.4 ± 25	43.9 ± 21.6	p=.023
Peak dose admin.	650 ± 124	384 ± 19	p=.002

Also, see Mawer G et al: Seizure 11:512-18, 2002

CIGARETTES (mg nicotine/day)

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

From Fried P et al: Neurotox Terat 25:427-436, 2003

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:

De Wals P et al: Paediat Perinat Epid 5:445-7, 1991
Johnson K et al: Teratology 49:375, 1994
Shapiro L et al: Lancet 350:1143-1144, 1997

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 . . . ."

Clewell III, HJ et al: A physiologically based pharmacokinetic model for retinoic acid and its metabolites. J Am Acad Dermatol 36:S77-S85, 1997.

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.

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

	SMOKING	BLACK	p	WHITE	p
ALL	never	--	--	--	--
	continuous	-264 gms	.05	-309	.06
MOTHER'S GENOTYPE					
1. CYPIAI	never	+24	.81	+63	.79
Aa/aa	continuous	-475	.007	-467	.05
(MSP1)					
2. GSTTI					
present	continuous	-61	.70	-291	.10
absent (deletion)	"	-594	.006	-579	.03

Wang X et al: JAMA 2002; 287:195-202.
Chong Y-C et al: J Occ Env Med 2003; 45:392-498

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 EFECTS ON LEARNING AND I.Q.
- NEED STUDIES OF AIRBORNE AND DERMAL EXPOSURS

HUMAN TERATOGENS: MECHANISMS OF ACTION

WARFARIN*:

INHIBITION OF VITAMIN K REDUCTASE

PROPYLTHIOURACIL**:

BLOCKS CONVERSION OF THYROXINE TO TRIIODOTHYRONINE

*Van Driel D et al: Teratology 66:127-140, 2002

**Rosenfeld H et al: Brit J Clin Pharm 68:609-617, 2009

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.

***Ludwig M: J Med Genet 42:289-291, 2005**
Cox GF et al: Am J Hum Genet 71:162-164, 2002

ANTICONVULSANTS: EFFECTS ON INTELLIGENCE

ISSUES:

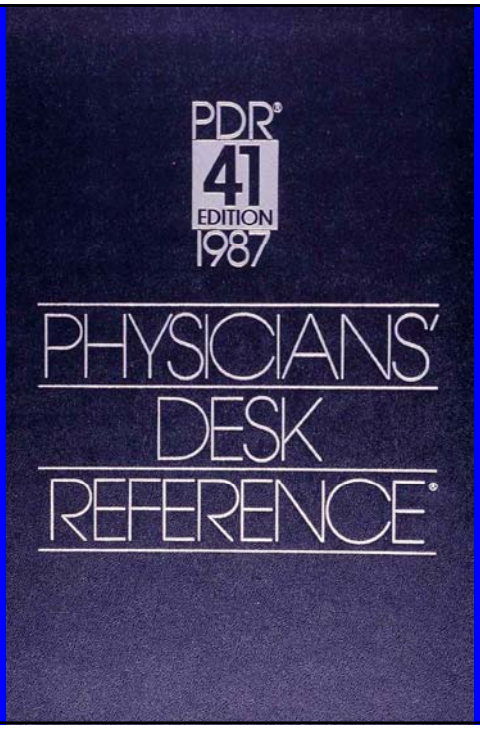
- **AGE OF CHILD**
- **TESTING INSTRUMENT**
- **TESTING PARENTS**
- **SELECTION OF MATCHED CONTROL**
- **EFFECT OF CONFOUNDERS, e.g. SES**

Domain	PB Effect	Significant p value (1-tailed)
Verbal Knowledge	Yes	0.035
Verbal Memory	No	
Perceptual Organization	Yes	0.054
Visual Memory	Yes	0.023
Distractibility	Yes	0.005
Drawing Ability	Yes	0.035
Motor Speed	No	

*** 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:

Friedman JM et al: Ob Gyn 75:594-599, 1990
Lo WY, Friedman JM: Ob Gyn 100:465-473, 2002
Public Affairs Comm (Teratology Society): Teratology 49:446-447, 1994.
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

Lo WY, Friedman JM: Am J Ob Gyn 2002; 100:465-473.

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.

	Bupropion - first trimester (n = 463)	Other antidepressants* first trimester (n = 3,241)
atrial septal defect (ASD)	0	4
coarctation	1	1
tetralogy of Fallot	0	1
transposition of great arteries	0	1
ventricular septal defect (VSD)	6	18
total (all defects)**	9	36

* fluoxetine, paroxetine, sertraline, citalopram

** not all specific defects listed

SSRIs AND HEART DEFECTS

Slone Birth Defects Study: Louik C et al: N Engl J Med 356:2675-2683, 2007.

	Paroxetine	Fluoxetine	Sertraline
Any heart defect	OR 1.4	0.9	1.5
	(0.2, 2.5)	(0.6, 1.5)	(0.9, 2.5)
Septal defects	0.8	1.2	2.0
	(0.3, 2.2)	(0.5, 2.2)	(1.2, 4.0)
RVOTD	3.3	1.0	2.0
	(1.3, 8.8)	(0.2, 3.4)	(0.6, 6.8)

No association with anencephaly, omphalocele or craniosynostosis

SSRIs AND HEART DEFECTS

CDC: National Birth Defects Prevention Study:
Alwan S et al: N Engl J Med 356:2684-2692, 2007.

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

Swan SH et al: Environ Health Persp 81:1056-1061, '05.

Salazar-Martinez E et al: Environmental Health 3:8-14, '04.

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

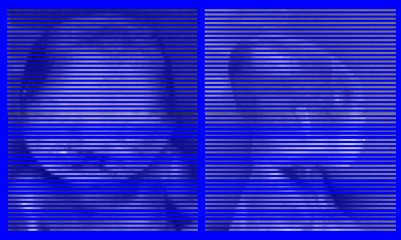
USE TO IDENTIFY HUMAN TERATOGENS

FALSE ALARMS:

- TOPICAL TRETINOIN → HOLOPROSENCEPHALY
  FRANZ ROSA
  NO: De Wals et al: Paediat Perinat Epid 5:445-7, 1991.

- STATINS →
  Edison RJ, Muenke M: N Engl J Med 350:1379-82, 1991
  NO: Petersen EE et al: AmJ Med Genet 146A:2701-5, 2008

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 ("Its 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

CRIDER KS ET AL: ARCH PEDIATR ADOL MED 163:978-985, 2009.

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-___-____.

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

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		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