HUMAN TERATOGENS: 2008 UPDATE

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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

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.

HUMAN TERATOGENS: 2007 - 2008

"NEW TERATOGENS": **mycophenolate mofetil (CellCept)**

lamotrigine (Lamictal)

severe nausea and vomiting of pregnancy

phthalates

MYCOPHENOLATE MOFETIL

Immunosuppressive agent: inhibitor of inosine mono-phosphate dehydrogenase; prevents do novo synthesis of geranosine nucleotides (see Allison AC, Eugui EM: Immunopharmacology 47:85-118, 2000).

Case reports: LeRay C et al: Obstet Gynecol 103:1091-94, 2004.

Case series: Sifontis NM et al: Transplantation 82:1698-1702, 2006.

MYCOPHENOLATE MOFETIL: PHENOTYPE OF MULTIPLE ANOMALIES

microtia, severe and bilateral

cleft lip and palate

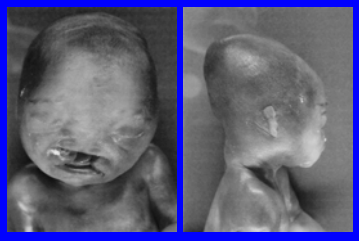
broad nasal bridge and hypertelorism

coloboma of retina

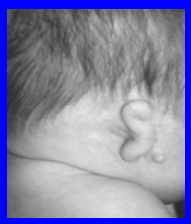
shortened digits and small nails

See: Perez-Aytes A et al: Am J Med Gen 146A:1-7, 2008.
Anderka M et al: Abstract #21, p. 297.

Selected MMF-Exposed Cases

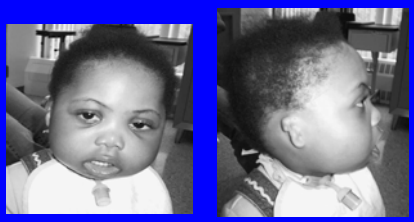


Le Ray et al., 2004



Tjeertes et al., 2007

Perez-Aytes et al. 2008



Velinov and Zellers, 2008.

MYCOPHENOLATE MOFETIL: QUESTION

Severe microtia: mycophenolate (CellCept)

thalidomide

13-cis retinoic acid

(Accutane)

LAMOTRIGINE:

anticonvulsant drug: inhibits release of glutamate and the voltage-sensitive sodium channel

clinical trials began in 1992; approved by FDA in 1994.

LAMOTRIGINE (LAMICTAL):

LAMOTRIGINE PREGNANCY REGISTRY: GLAXOSMITHKLINE

- lamotrigine monotherapy (n=414): 2.9% (95CI 1.6-5.1%)
- lamotrigine + valproate (n=88): 12.5% (95CI 6.7-21.7%)
- lamotrigine + other (n=182): 2.7% (95CI 1.0-6.6%)

no controls; use CDC data: 2% at birth
no study exam

Contact: Paige Churchill, Project Manager
paige.churchill@inveresk.com; Inveresk 1-800-336-2176

Cunnington M et al: Neurol 64:955-60, 2005

LAMOTRIGINE, GABAPENTIN, TOPIRAMATE

U.K. EPILEPSY AND PREGNANCY REGISTER*

	Number of Women	Number of Malformations	Rate
CARBAMAZEPINE	900	20	2.2% (1.4-3.4)
VALPROATE	715	44	6.2% (4.6-8.2)
LAMOTRIGINE	647	21	3.2% (2.1-4.9)
PHENYTOIN	82	3	3.7% (1.3-10.2)
GABAPENTIN	31	1	3.2% (0.6-16.2)
TOPIRAMATE	28	2	7.1% (2.-22.6)
LEVETIRACETAM	22	0	0.% (0-14.9)

*Morrow J et al: J Neurol Neurosurg Psych 77:193-8, 2006.

AED PREGNANCY REGISTRY:
(AED = antiepileptic drugs)

- **WOMEN ON ANTICONVULSANTS IN NORTH AMERICA AND CANADA**
  CALL TOLL-FREE 1-888-233-2334
  (www.AEDPregnancyregistry.org)
- **INFORMED CONSENT**
- **3 INTERVIEWS:** **ENROLLMENT**
  Demographics, Confounders
  7-MONTHS GESTATION
  Change in dosage, U/S findings
  POSTPARTUM
  Health of infant
- **OBTAIN WRITTEN RELEASES FOR NEUROLOGIST OR PSYCHIATRIST AND PEDIATRICIAN**

LAMOTRIGINE (LTG) – EXPOSED: MAJOR MALFORMATIONS

19/684 : MAJOR MALFORMATIONS
2.8% (95 CI:1.7-4.3)

16/684 (2.3%) : IDENTIFIED AT BIRTH (0 to 5 days of age)
not increased significantly vs. unexposed controls (1.62%)

Relative Risk 1.4 (95 CI: 0.9-2.3)

(Comparison population: Brigham and Women's Hospital: Nelson K, Holmes LB: NEJM 320:19-23, 1989)

LAMOTRIGINE MONOTHERAPY-EXPOSED: ORAL CLEFTS

Study #	Phenotype*	mg First Trimester	Folic Acid Suppl at Conception	Cigarette Smoking
1779	Cleft lip, unilateral	400 mg	Yes	No
2389	Cleft palate	300	Yes	No
3036	Cleft palate	500	Yes	No
4557	Cleft palate	100	Yes	No
5638	Cleft lip & palate	125	Yes	No

* None considered syndromic; negative family history

PREVALENCE: 5/684 = 1:137 or 7.3/1,000

LAMOTRIGINE MONOTHERAPY-EXPOSED	UNEXPOSED COMPARISON POPULATION
5/684 or 7.3/1,000	0.7 / 1,000

$\frac{7.3}{0.7}$ = 10.4 X increase (95 CI 4.3 – 24.9)

Holmes LB et al: Neurology 70:2152-8, 2008

Anticonvulsant Drugs and Oral Clefts

	Relative Risk
Lamotrigine (n = 952)	9.1
Valproate (n = 303)	20.1
Phenobarbital (n = 189)	32.4
Carbamazepine (n = 913)	20.9

Question: Common mechanism or different mechanisms?

LAMOTRIGINE MONOTHERAPY-EXPOSED: OTHER SOURCES

	NUMBER WOMEN	TOTAL MALFORMATIONS	ORAL CLEFTS
GSK INTERNAT. LTG REGISTRY	707	2.7%	1 CP; 1 CLP
UK EPILEPSY PREG. REGISTER	647	3.2	1 CLP
SWEDISH MEDICAL BIRTH REGISTRY	90	4.4	1 CP
AUSTRALIAN PREG. REGISTRY	128	0	0
DANISH REGISTRY	51	2	0
	1,623		4 (2.5/1,000)

2.5
0.7 = 3.6 RR

NUTRITIONAL DEFICIENCIES IN PREGNANCY: CASE REPORTS

PHENOTYPES: MID-FACE HYPOPLASIA (BINDER ANOMALY)

ANENCEPHALY – SPINA BIFIDA

CLINICAL STORIES: POST-BARIATRIC SURGERY

CHRONIC DIARRHEA, MALABSORPTION, WEIGHT LOSS

HYPEREMESIS GRAVIDARUM

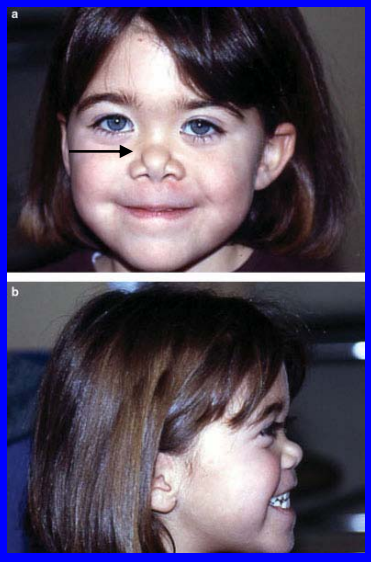
Menger H et al: Am J Med Genet 72:129-134, 1997.
Robinson JN et al: Ob Gyn 92:673-675, 1998.
Brunetti-Pierri N et al: Am J Med Genet 1437: 673-675, 1998.

BILIARY LITHIASIS EARLY IN PREGNANCY

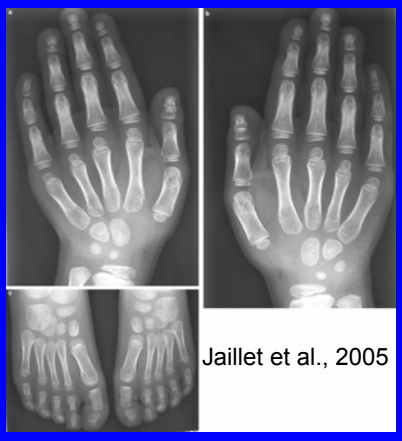
Jaillet J et al: BDR(A): Clin Mol Teratol 73:188-193, 2005.

(Courtesy of Angela E. Lin, M.D.)

MATERNAL VITAMIN K DEFICIENCY: Additional reports



"Drumstick-like distal phalanges"



Jaillet et al., 2005

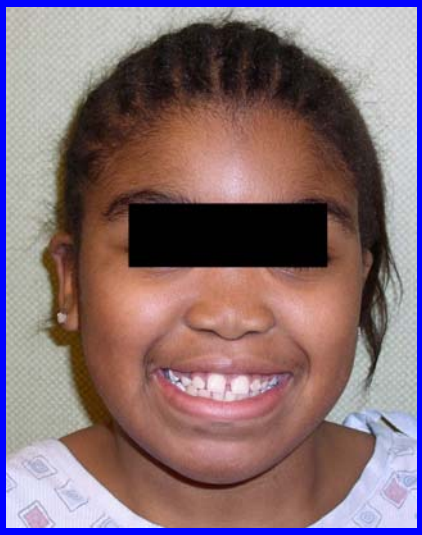
NEW PATIENT (I) MOTHER

BWH: 22 yo healthy African American G2

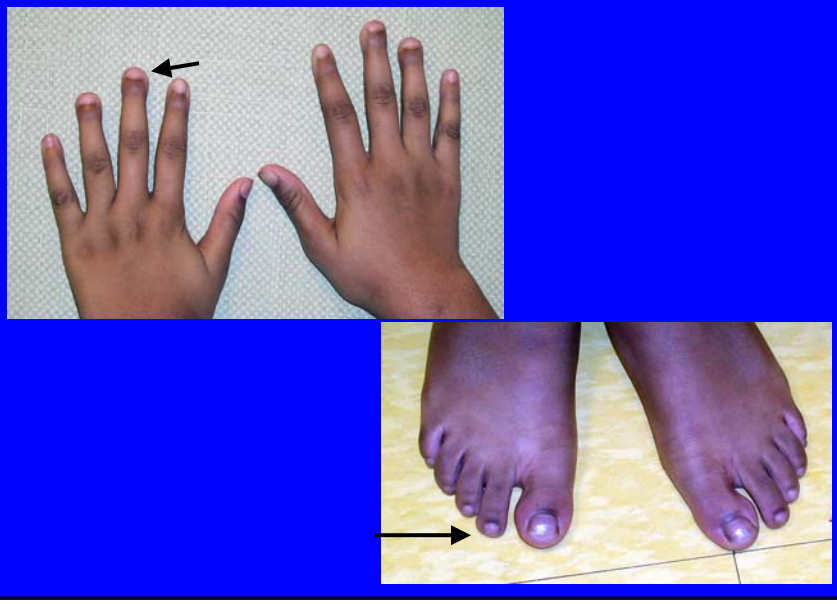
7 wks: Severe hyperemesis gravidarum, Compazine
185/200 lbs → 169 (16% loss) (→ 193)
Admitted after 4th visit (10 wks): Haldol, IVF, chewable vitamins

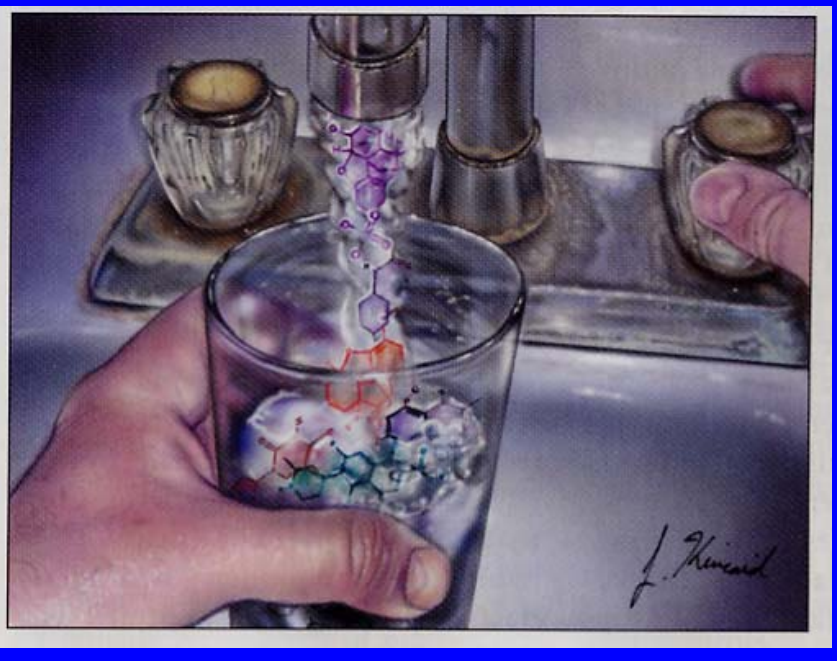
Admitted after 7th visit (15 wks): Haldol, IVF, Mg supplement
- Profuse epistaxis, required packing, cautery.
- Labs: Bleeding disorder
  - ↓ K, Mg, II, VII, IX, X.
  - Prolonged PT, APTT.
- Treatment:
  - TPN, IV hydration, electrolyte replacement
  - Vitamin K 10 mg subcutaneous/day x3 days
  - Coagulopathy normalized over 10 days
- Robinson et al., Obstet Gynecol, 1998.
  - Coagulopathy secondary to Vit K deficiency in hyperemesis

MATERNAL VITAMIN K DEFICIENCY
Hyperemesis gravidarum



MATERNAL VITAMIN K DEFICIENCY
Hyperemesis gravidarum





PHTHALATES: **plasticizers, ? endocrine disruptor**

1. **Salazar-Martinez E et al: Environ Health 3:8-14, 2004. Effect on anogenital (AG) distance in humans**
2. **Swan SH et al: Environ Health Perspectives: 113:1056-1061, 2005.**

   Increases levels in urine of mothers; decreases AG distance
3. **Sathyanarayana S et al: Pediatrics 121:e260-e268, 2008.**

Developmental effects of phthalates

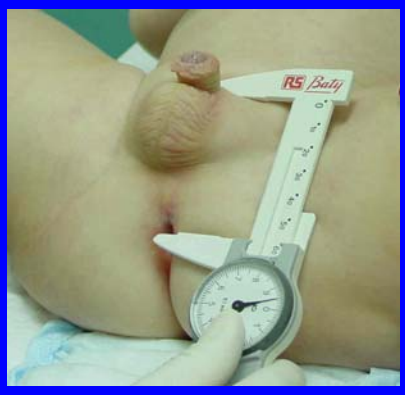
- Disrupts fetal testis testosterone biosynthesis
  - Decreased gene expression and protein levels
    - Lipid transport (Scarb1 and Star)
    - Steroidogenic pathway (CYP11A1, HSDB1, CYP17A1)
- Decreased insulin-like factor 3 gene expression

Manifestations:

Cryptorchidism and Hypospadias

Reduced anogenital distance (feminization of perineum)

Measuring Anogenital Distance



This is similar to the toxicological measure
AGD is repeatable (CV =7.2%)

HUMAN TERATOGENS: 2007 - 2008

Controversies: SSRIs, in general

Paroxetine (Paxil), in particular

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 EPIDEMIOLOGIC STUDY:

RATIONALE: Possible "signal" for heart defects, esp. ventricular outflow tract, in GSK Bupropion Pregnancy Registry spontaneous reports from health care providers.

GOAL: 1) Prevalence of heart defects in infants born to women taking bupropion.

2) Prevalence in infants exposed to other anti-depressants, including paroxetine

INGENIX STUDY: http://ctr.gsk.co.uk/welcome.asp

OR for congenital malformation according to ever use of specific antidepressants during the first trimester, cohort analysis, RDB

Antidepressant	n	Total	Prev per 1000	OR*	
				Crude (95% CI)	Adjusted** (95% CI)
Amitriptyline	4	233	17.2	0.65 (0.24, 1.78)	0.68 (0.25, 1.89)
Amitriptyline / Chlordiazepoxide	0	5	0	0	0
Amitriptyline / Perphenazine	0	1	0	0	0
Bupropion	15	463	32.4	1.32 (0.76, 2.32)	1.23 (0.70, 2.17)
Citalopram	10	298	33.6	1.36 (0.70, 2.64)	1.23 (0.62, 2.45)
Clomipramine	0	5	0	0	0
Desipramine	0	10	0	0	0
Doxepin	0	22	0	0	0
Fluoxetine	31	1178	26.3	1.04 (0.67, 1.61)	1.03 (0.67, 1.60)
Fluvoxamine	0	26	0	0	0
Imipramine	2	42	47.6	1.92 (0.46, 8.06)	1.97 (0.46, 8.40)
Mirtazapine	0	23	0	0	0
Nefazodone	1	75	13.3	0.51 (0.07, 3.70)	0.49 (0.07, 3.58)
Nortriptyline	1	87	11.5	0.44 (0.06, 3.16)	0.47 (0.06, 3.41)
Paroxetine	27	704	38.4	1.72 (1.09, 2.71)	1.84 (1.16, 2.91)
Protriptyline	0	4	0	0	0
Sertraline	12	705	17.0	0.61 (0.33, 1.12)	0.58 (0.31, 1.08)
Trazodone	3	154	19.5	0.75 (0.23, 2.39)	0.70 (0.21, 2.30)
Trimipramine	0	1	0	0	0
Venlafaxine	6	215	27.9	1.10 (0.47, 2.54)	1.05 (0.45, 2.45)

Prevalence per 1,000 live born infants

* Reference group for OR calculations is all other antidepressants.

** Adjusted for age, calendar year of delivery, dispensing of lithium, dispensing of carbamazepine, diagnosis of pre-eclampsia or eclampsia, and infant sex.

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 hearts, all SSRIs – no associaton

	Paroxetine
RVOTO:	OR 2.5
	(1.0, 6.0)

positive association with anencephaly, omphalocele craniosynostosis

VENTRICULAR SEPTAL DEFECT, MUSCULAR TYPE

1,053 CONSECUTIVE NEONATES: NAHARIYA, ISRAEL

APRIL TO SEPTEMBER, 1994

COLOR DOPPLER ECHOCARDIOGRAPHY

- AGES 6 TO 170 HOURS OLD (mean 37)

56/1,053 HAD MUSCULAR VSD: 1 to 5mm

10% HAD SYSTOLIC MURMUR

89% CLOSED SPONTANEOUSLY

Roguin N et al: JACC 26:1545-8, 1995.

SSRIs: PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

SLONE EPIDEMIOLOGY CENTER, BOSTON UNIVERSITY

1998-2003: 377 PPHN

836 CONTROLS

SSRI EXPOSURE: 14 PPHN

6 CONTROLS

ODDS RATIO: 6.1 (95 CI: 2.2-16.8)

Chambers CD et al: N Engl J Med 354:579-87, 2006.

SSRIs: NEONATAL WITHDRAWAL SYNDROME

MEDLINE AND PSYCINFO SEARCH: 1966-2005

LATE EXPOSURE: RISK RATIO 3.0 (95 CI:2.0-4.4)

TREATMENT: SIGNS MILD; SUPPORTIVE CARE; DISAPPEARS BY TWO WEEKS OF AGE

From Moses-Kolko EL et al: JAMA 293:2372-83, 2005.

OTHER TOPICS: ANNUAL UPDATE, 2009

- PESTICIDES
- BISPHENOL A
- STATINS
- GENE-ENVIRONMENT INTERACTIONS
- REVISION OF DRUG CATEGORIES A, B, C, D and X
- AIRBORNE EXPOSURES
- DERMAL EXPOSURES

SPECIAL THANKS TO MARLENE ANDERKA, ANGELA LIN, RUSS HAUSER and ALLEN MITCHELL WHO PROVIDED SLIDES OR DATA TABULATIONS FOR THIS REVIEW.