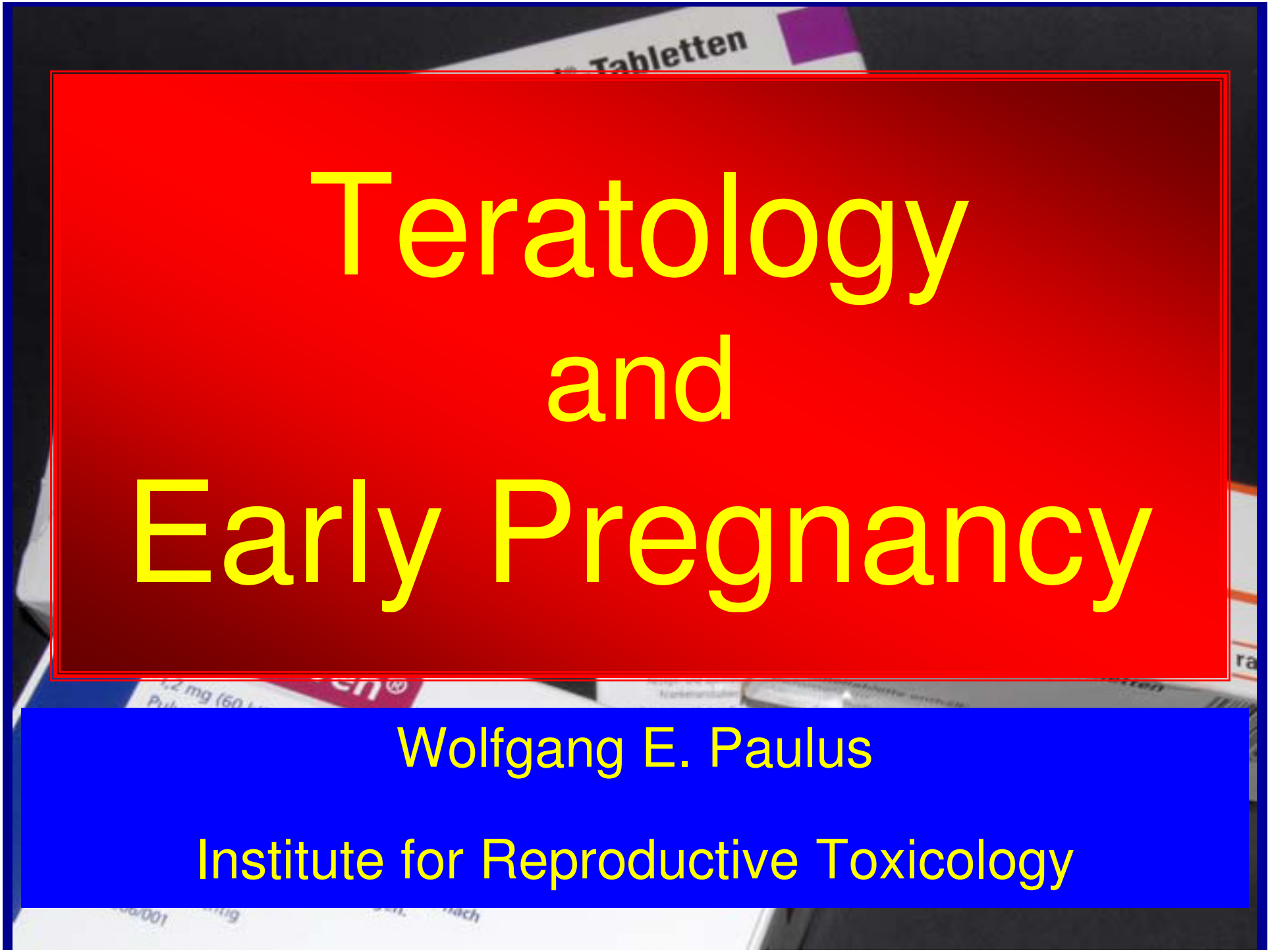

Teratology and Early Pregnancy

Wolfgang E. Paulus

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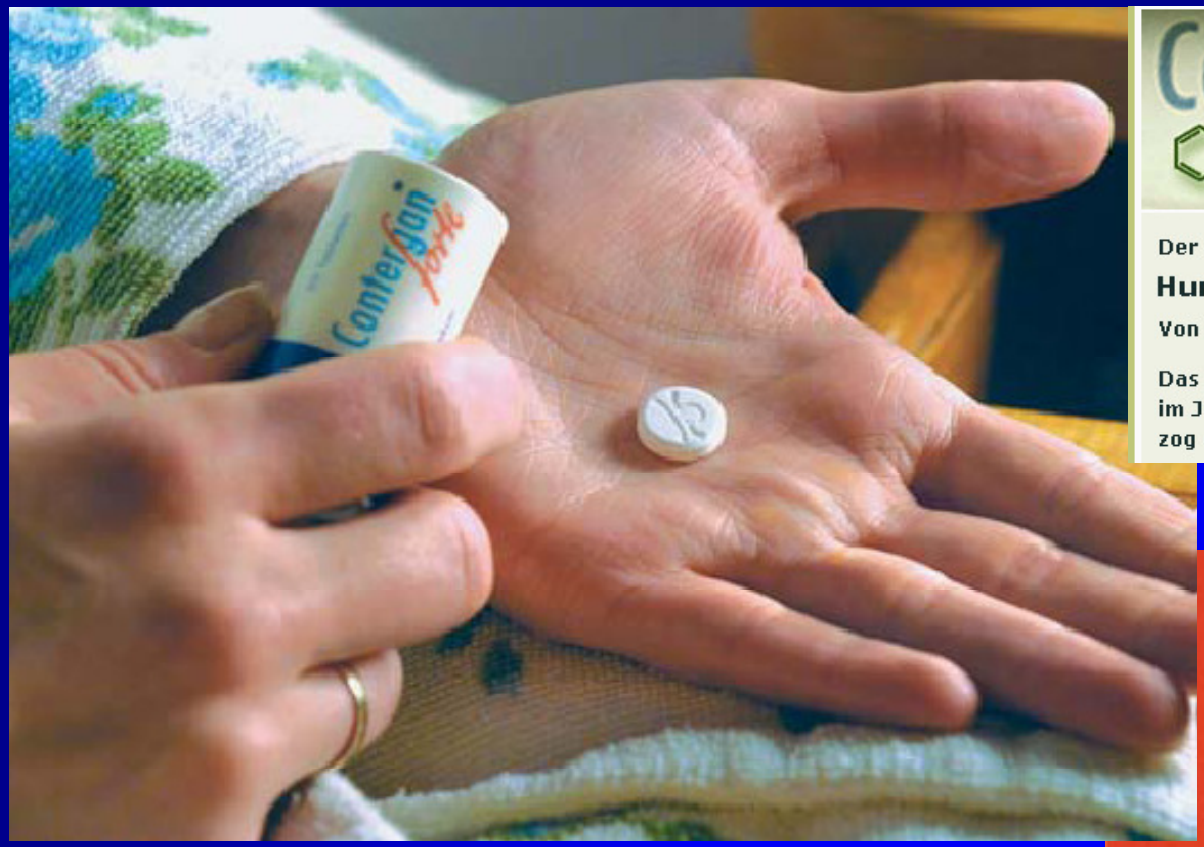
Produit de la France
Cognac
fine Champagne
BOSFORD
EXTRA DRY
GIN
CYNAR
CYNAR



Der lange Weg zum Arzneimittelgesetz in Deutschland

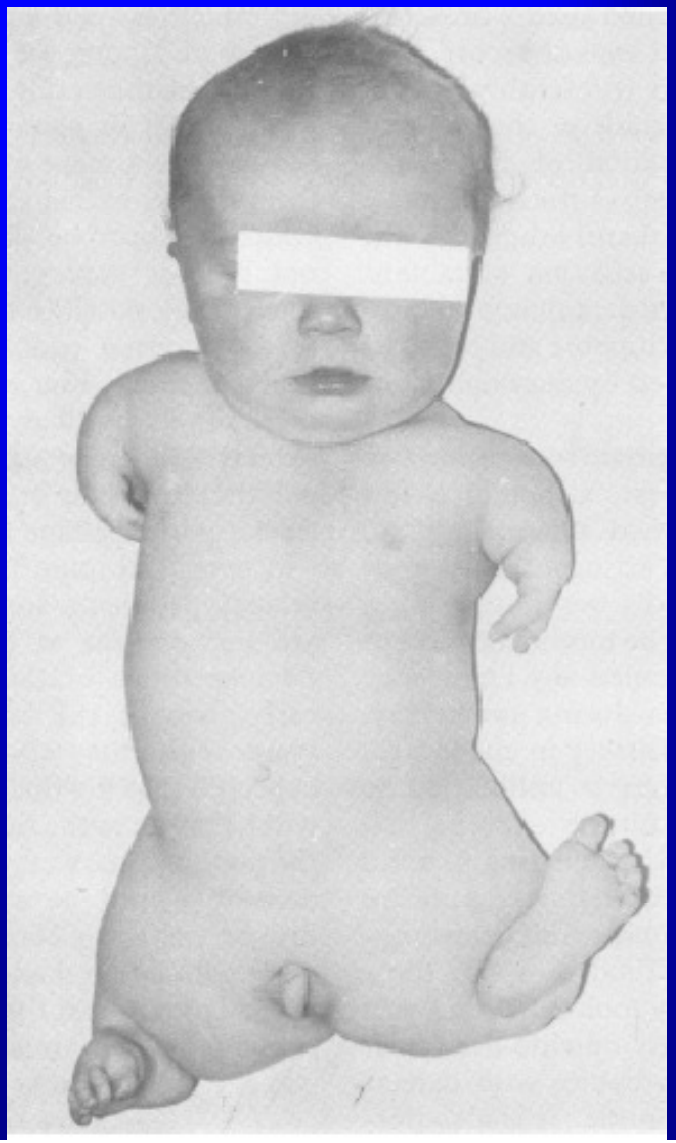
Hundert Jahre Gesetzeslücke

Von Gregor Taxacher

Das erste deutsche Arzneimittelgesetz wurde 1961 beschlossen - im Jahr des Contergan-Skandals. Die Lehren aus der Katastrophe zog der Gesetzgeber aber erst fünfzehn Jahre später.

Thalidomide Disaster

Severe limb reduction defects of about 10,000 children after maternal medication with thalidomide between 1958 and 1962

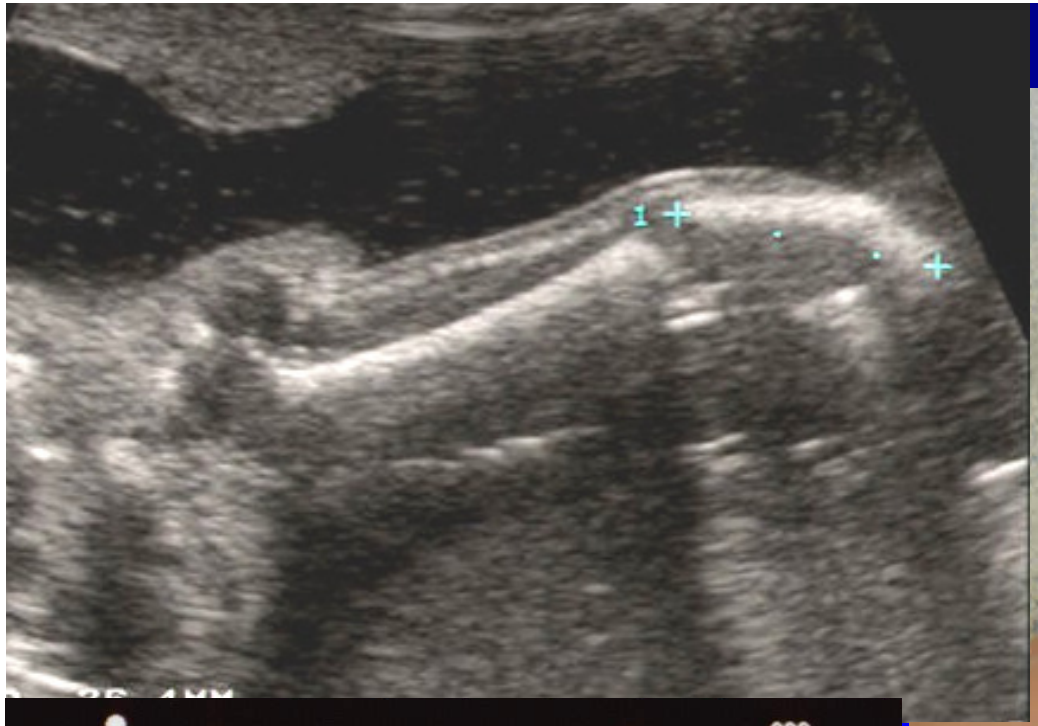


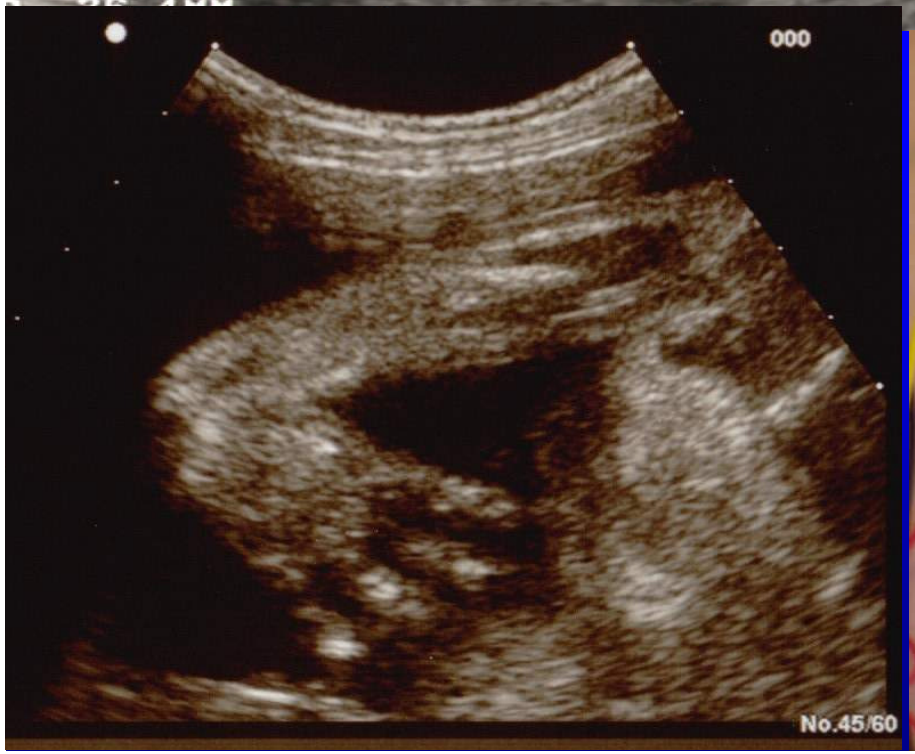
Safety Warnings

Safety warnings on package leaflets or in pharmacopoeias are often general and outdated

→ protection of the drug producer from litigation cases

prevention of elective pregnancy terminations due to misperception of teratogenic risk!!

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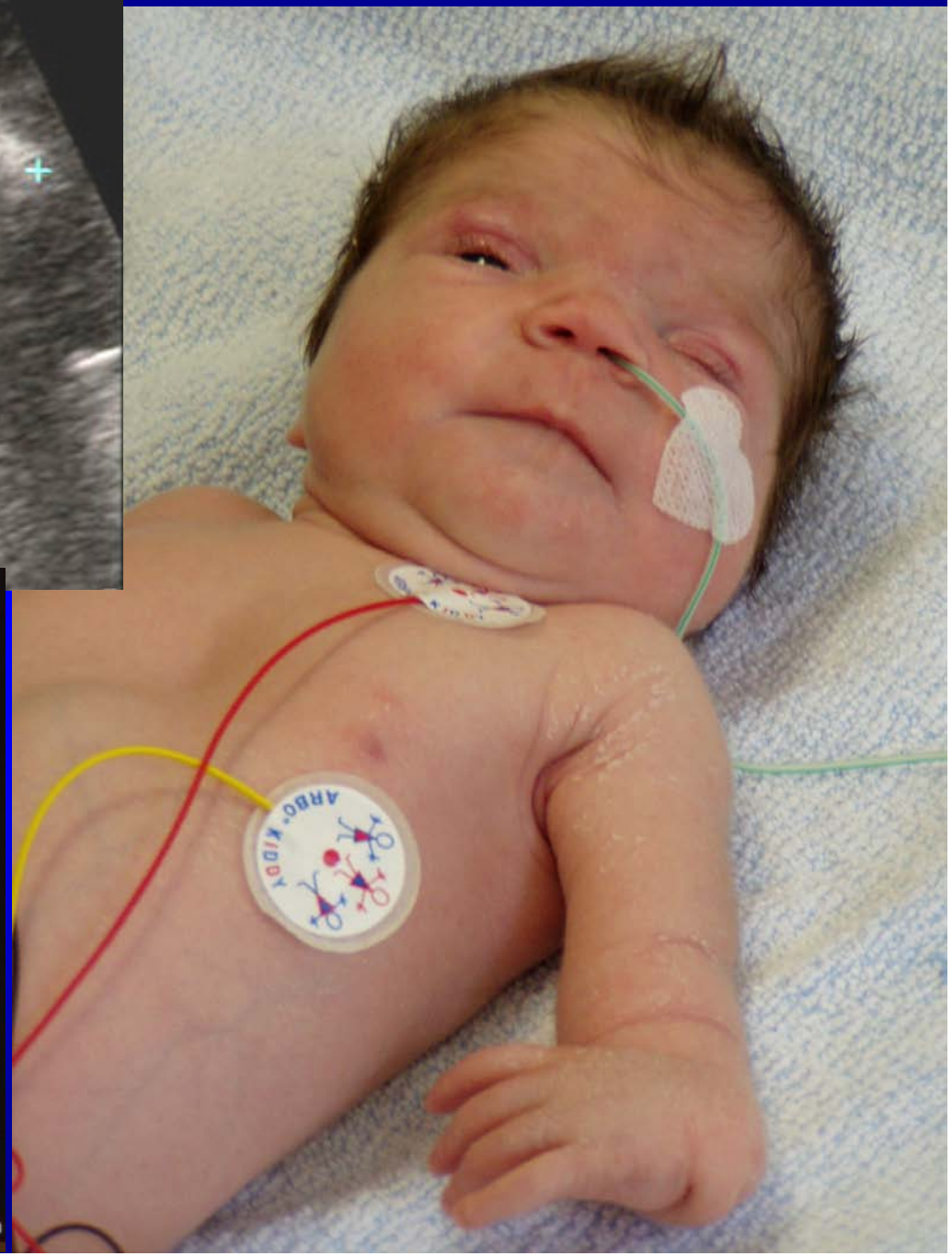
No.45/60




European
Network
Teratology
Information
Services

ENTIS

TIS in Europe, Israel and Latin America collaborate in the European Network of Teratology Information Services (ENTIS) in order to optimize

- interpretation of risk data
- risk communication
- risk management
- recommendations for drug treatment in pregnant women

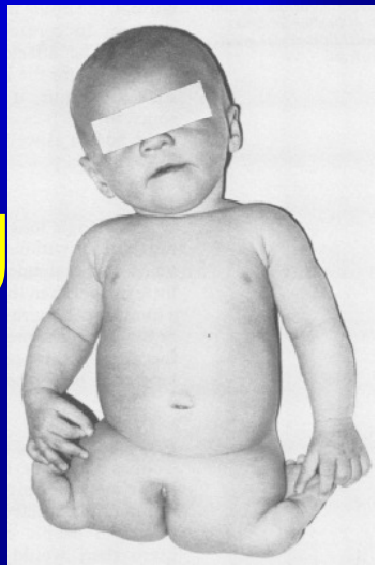
What´s a teratogen?

Any medication, chemical, infectious disease, or environmental agent that might interfere with the normal development of a fetus and result in the loss of a pregnancy, a birth defect or a pregnancy complication.

Congenital Anomalies

Congenital defects may occur in 5% of all births, and relate to

- structural, anatomic alterations,
- metabolic disorders
- functional defects (including mental retardation)



Cause of Human Congenital Malformations

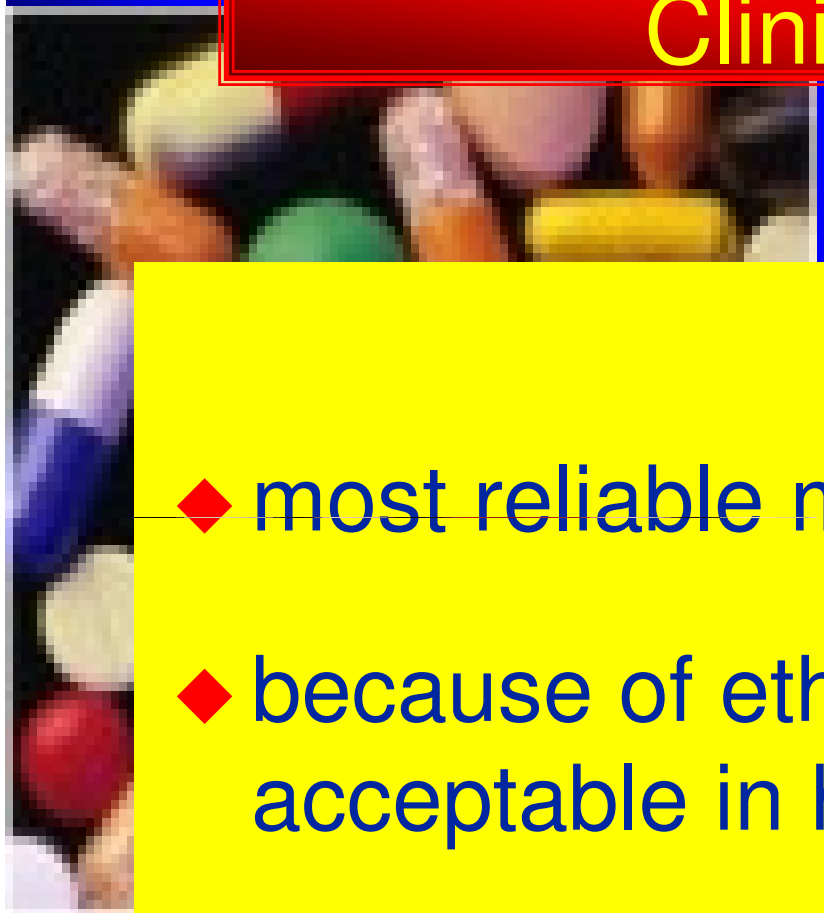
monogenetic conditions	8 - 9%
chromosomal disorders	6 - 8%
environmental influence	2 - 5%
infectious agents: rubella, toxoplasmosis, cytomegalovirus, varicella	1 - 2%
maternal diseases (i. e. diabetes, epilepsy, phenylketonuria)	0.7 - 1.7%
prescription drugs	0.2 - 1.3%
multifactorial disorders	20 - 49%
unknown causes	34 - 62%

Kalter & Warkany 1983; Rösch u. Steinbicker 2003

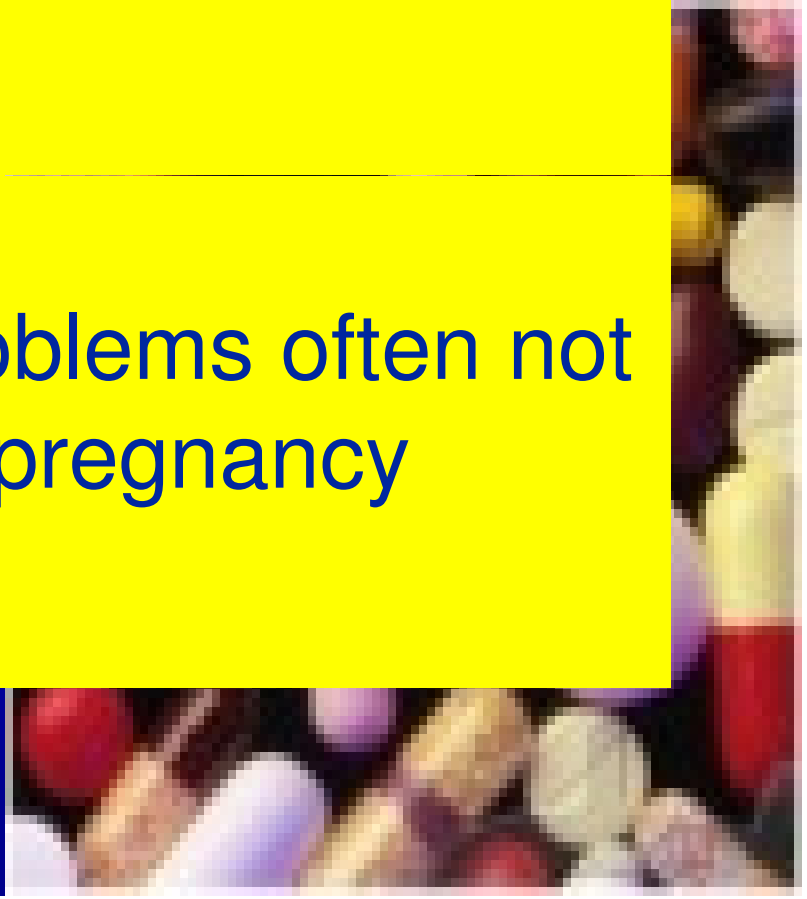
Evaluation of Teratogenic Risk
Animal Models

- Teratogenic potential is first tested in animal models by means of reproductive toxicology studies
- Different metabolism of medication in animals (genetic determination!)
- Some drugs, due to the high dosages employed, can prove teratogenic in some animal species but not in humans (e.g. glucocorticoids)

Evaluation of Teratogenic Risk Clinical Studies



- most reliable method
- because of ethical problems often not acceptable in human pregnancy



Evaluation of Teratogenic Risk
Observational Cohort Studies

- Follow up of accidental exposure in early pregnancy
- Results after a long period of data collection
- Prospective methodology minimizes recall bias of the studied drugs

Database FETIS

- beginning of enrollment: 1988
- documentation of more than 45,000 cases
- > 20,000 cases with complete follow up of pregnancy

Data Sampling

- prospective collection of data after call at our Teratology Information Service (TIS)
- risk evaluation after accidental exposure in early pregnancy
- last examination of children: not earlier than 6 weeks after birth

Fisher´s Exact Test

test of differences in the rates of fetal loss and congenital malformations

exposed cases

control group

not or not seriously exposed cases of our TIS

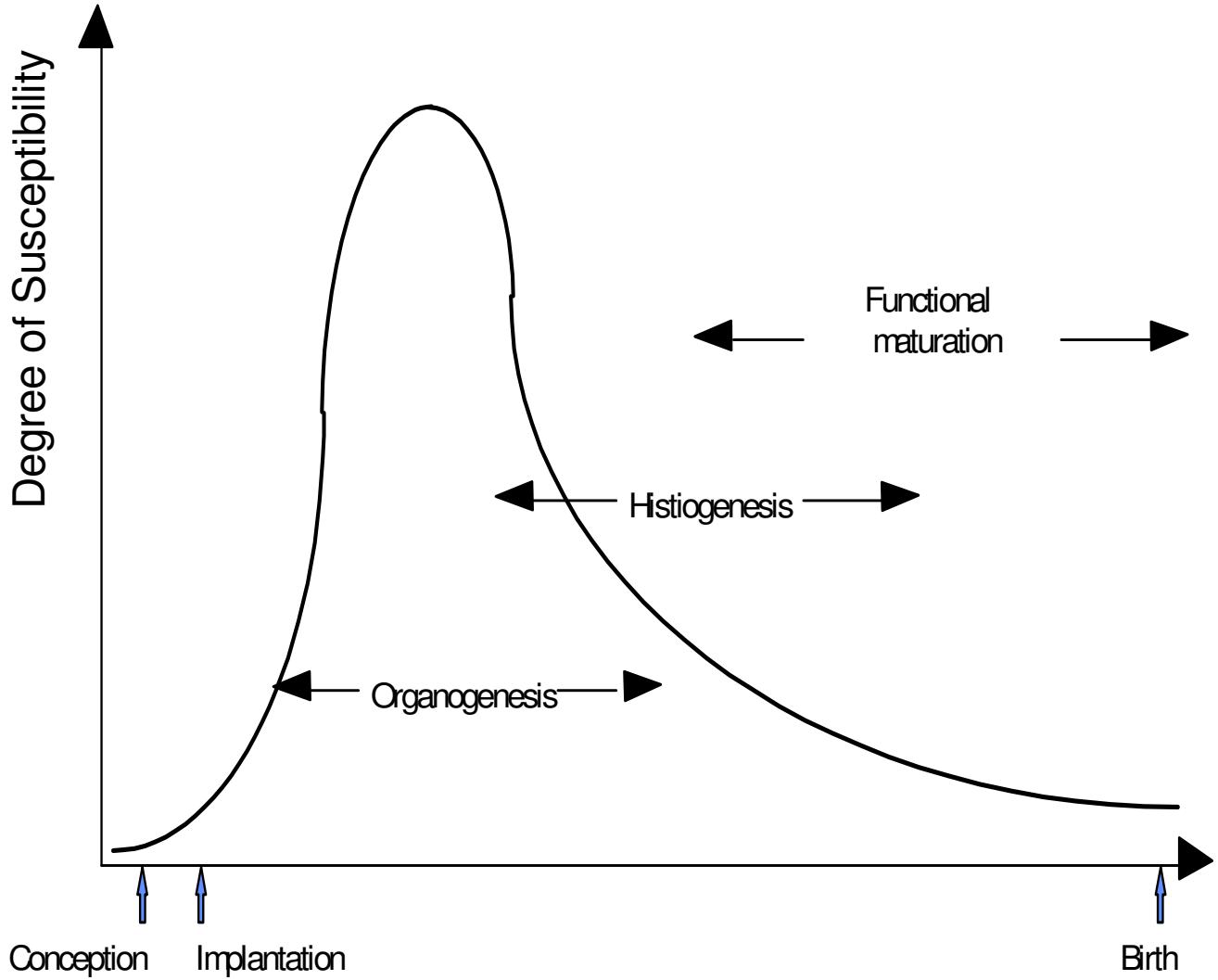
Principles of Teratology

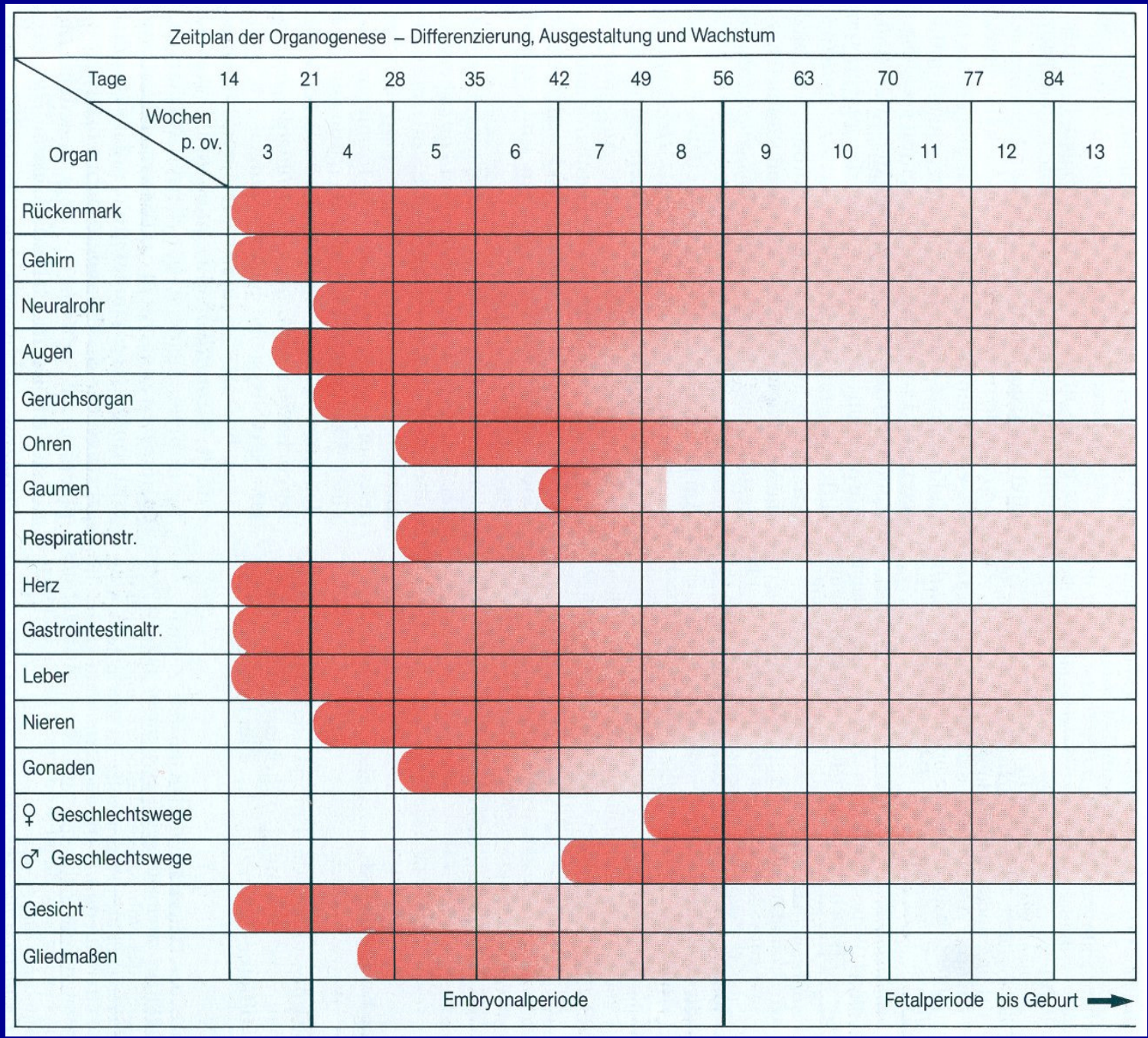
Susceptibility to teratogens depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.

Principles of Teratology

Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.

Stages of Susceptibility




Zeitplan der Organogenese – Differenzierung, Ausgestaltung und Wachstum
Tage
14
21
28
35
42
49
56
63
70
77
84
Wochen p. ov.
Organ
3
4
5
6
7
8
9
10
11
12
13
Rückenmark
Gehirn
Neuralrohr
Augen
Geruchsorgan
Ohren
Gaumen
Respirationstr.
Herz
Gastrointestinaltr.
Leber
Nieren
Gonaden
♀ Geschlechtswege
♂ Geschlechtswege
Gesicht
Gliedmaßen
Embryonalperiode
Fetalperiode bis Geburt

Principles of Teratology

The final manifestations of abnormal development are

- death („all-or-none” phenomenon)
- malformation
- growth retardation
- functional disorder
- transplacental carcinogenesis

Principles of Teratology

The access of adverse environmental influences to developing tissue depends on the nature of the influences (agent).

Principles of Teratology

Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level.

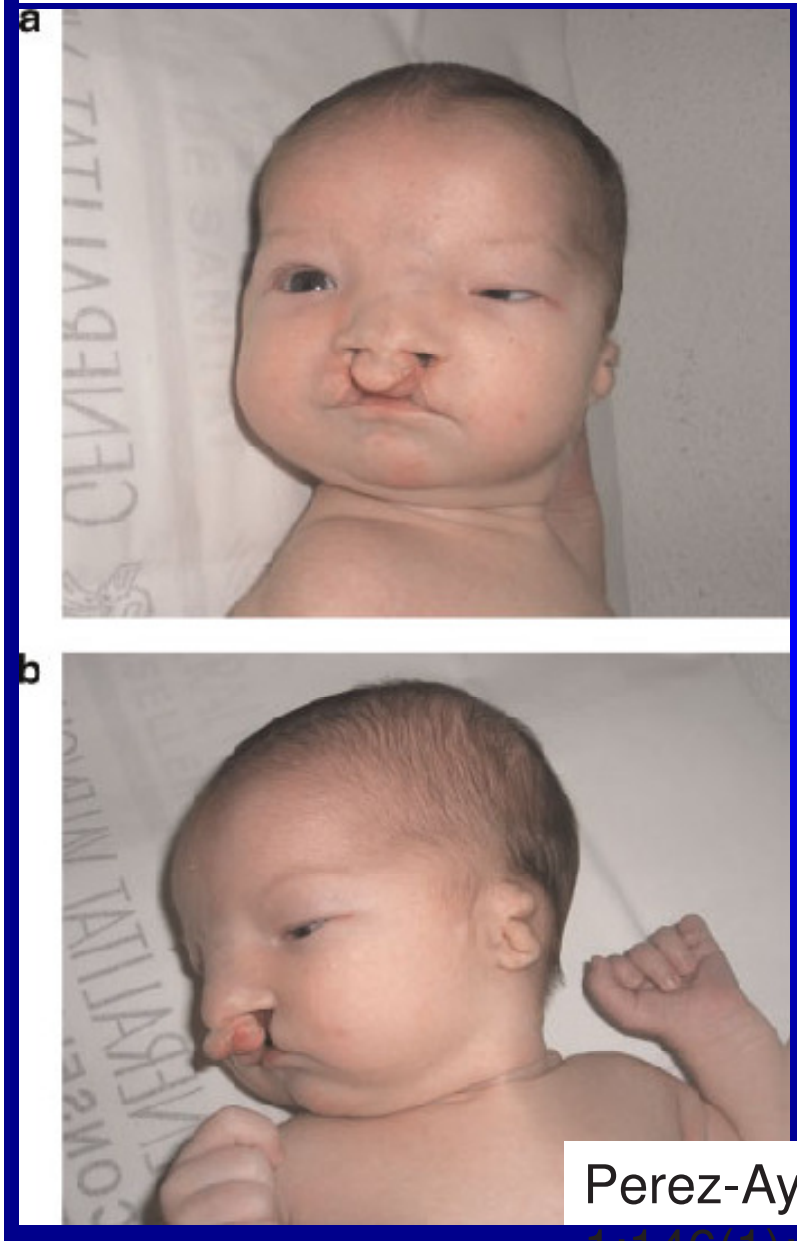
Teratogenic agents in the first trimester (1)

Agent	**Anomaly**
Ethanol	multiple defects
Aminoglycosides	renal damage
Androgens	masculinization (> wk 7 p.m.)
Antiepileptics - Carbamazepine - Valproic acid	multiple defects esp. neural tube defects esp. neural tube defects
Ergotamine	intestinal atresia, cerebral atrophy, multiple arthrogryposis
Coumarin derivatives (Phenprocoumon, Warfarin)	multiple defects (exposure > wk 8 p.m.)

Teratogenic agents in the first trimester (2)

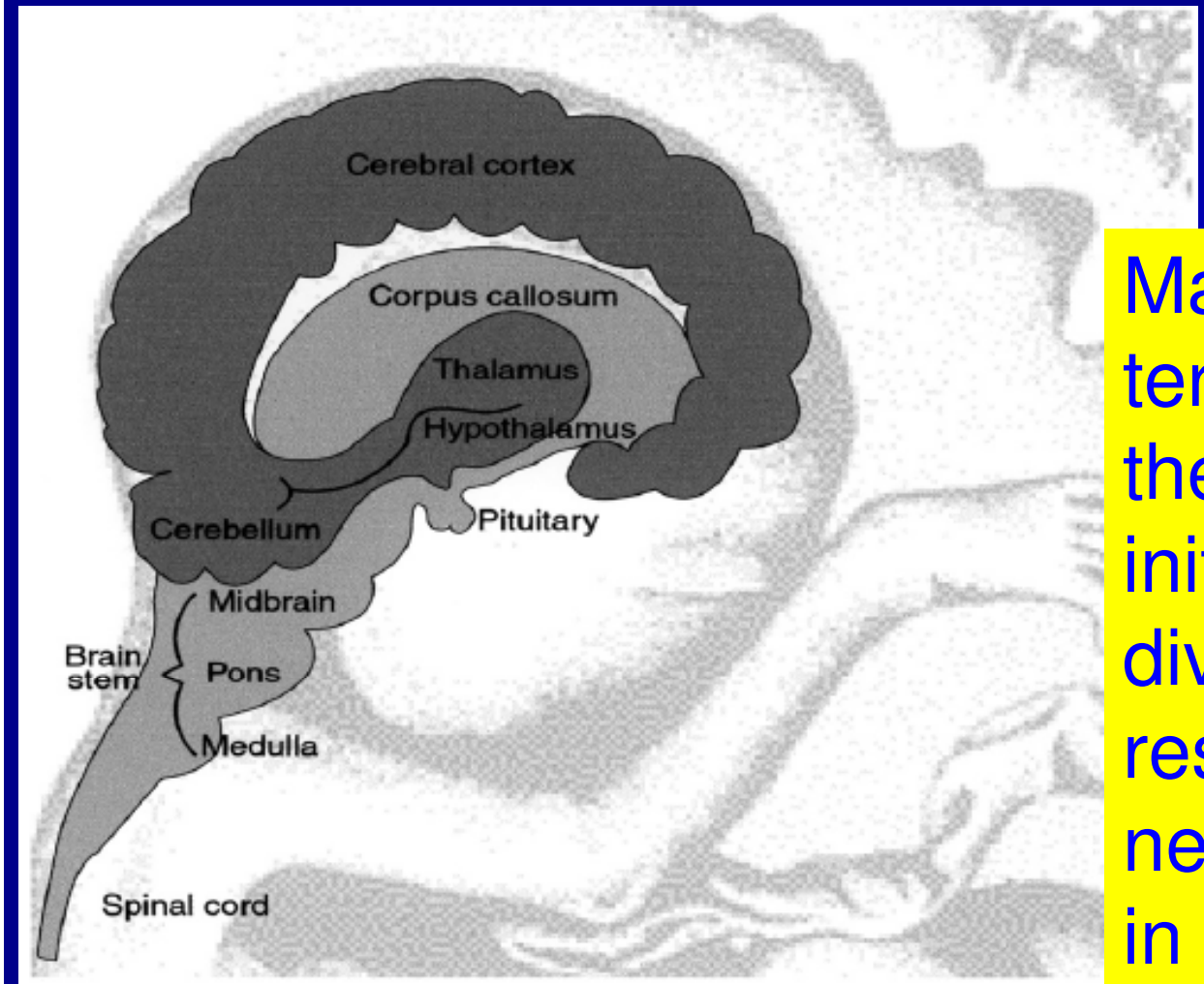
Agent	**Anomaly**
Lithium	cardiovascular defects (according to new data low risk)
Misoprostol	Moebius syndrome (anomalies of limbs and CNS)
Penicillamin	Cutis laxa (low risk!)
Radionuclides	multiple defects
Retinoids / Vitamin A (>25.000 IE/d)	multiple defects
Mycophenolate Mofetil	microtia, auditory canal atresia, cleft lip/palate, micrognathia, hypertelorism
Thalidomide	limb malformations

In Utero Exposure to Mycophenolate Mofetil:
A Characteristic Phenotype?

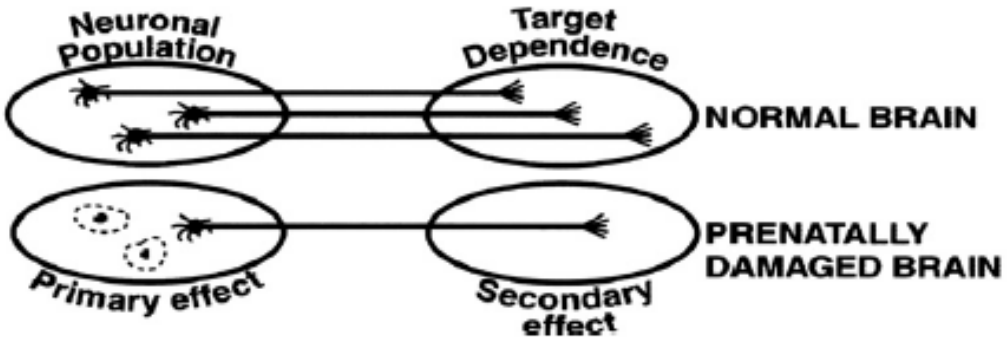


- cleft lip/palate
- microtia
- auditory canal atresia
- micrognathia
- hypertelorism

Perez-Aytes et al. Am J Med Genet A. 2008 Jan



Many CNS targeting teratogens exert their toxic effects by initially killing dividing cells resulting in reduced neuronal populations in the mature brain.



Pollard. Fetal Neonatal Med 2007

Fetal Alcohol Syndrome (FAS)

- pre- and postnatal growth deficiencies
- craniofacial anomalies
- intellectual disabilities
- behaviour problems

Guerri C, Bazinet A, Riley EP. Foetal Alcohol Spectrum Disorders and alterations in brain and behaviour. Alcohol Alcohol. 2009;44(2):108-14

dysplasia of the auricle

microcephaly

blepharophimosis

short upturned nose

smooth philtrum

thin upper lip

microgenia

Dosage of Alcohol

- FAS: 30% to 45% after daily intake of 140 g ethanol (about 1.5 l of wine)
- wide range of dosage (FAS after daily intake of 60 g ethanol!)
- reduced birth weight after daily intake of 24 g ethanol
- neurological deficits after binge drinking (e. g. 60 g ethanol)
- No threshold for damage!!

Jones 1974, Streissguth et al. 1992

Disorders of bahaviour after intrauterine exposure with psychotropic drugs ?

- conflicting results of animal experiments regarding behaviour and learning
- influence of psychotropic drugs on transmitters in the CNS
- irreversible damage of CNS development?

Antiepileptics

Incidence:
1of 250 pregnancies

Lindhout 1994

Antiepileptics

- Baseline rate of congenital malformations:
  - ➡ 3 - 5 %
- Risk of congenital malformations with antiepileptic therapy:
  - ➡ 7 - 10 %

Lindhout 1994

ORIGINAL CONTRIBUTION

Affect of Seizures During Gestation on Pregnancy Outcomes in Women With Epilepsy

Yi-Hua Chen, PhD; Hung-Yi Chiou, PhD; Herng-Ching Lin, PhD; Hsiu-Li Lin, MD

	OR [95%CI]
low birth weight	1.36 [1.01-1.88]
preterm delivery	1.63 [1.21-2.19]
SGA	1.37 [1.09-1.70]

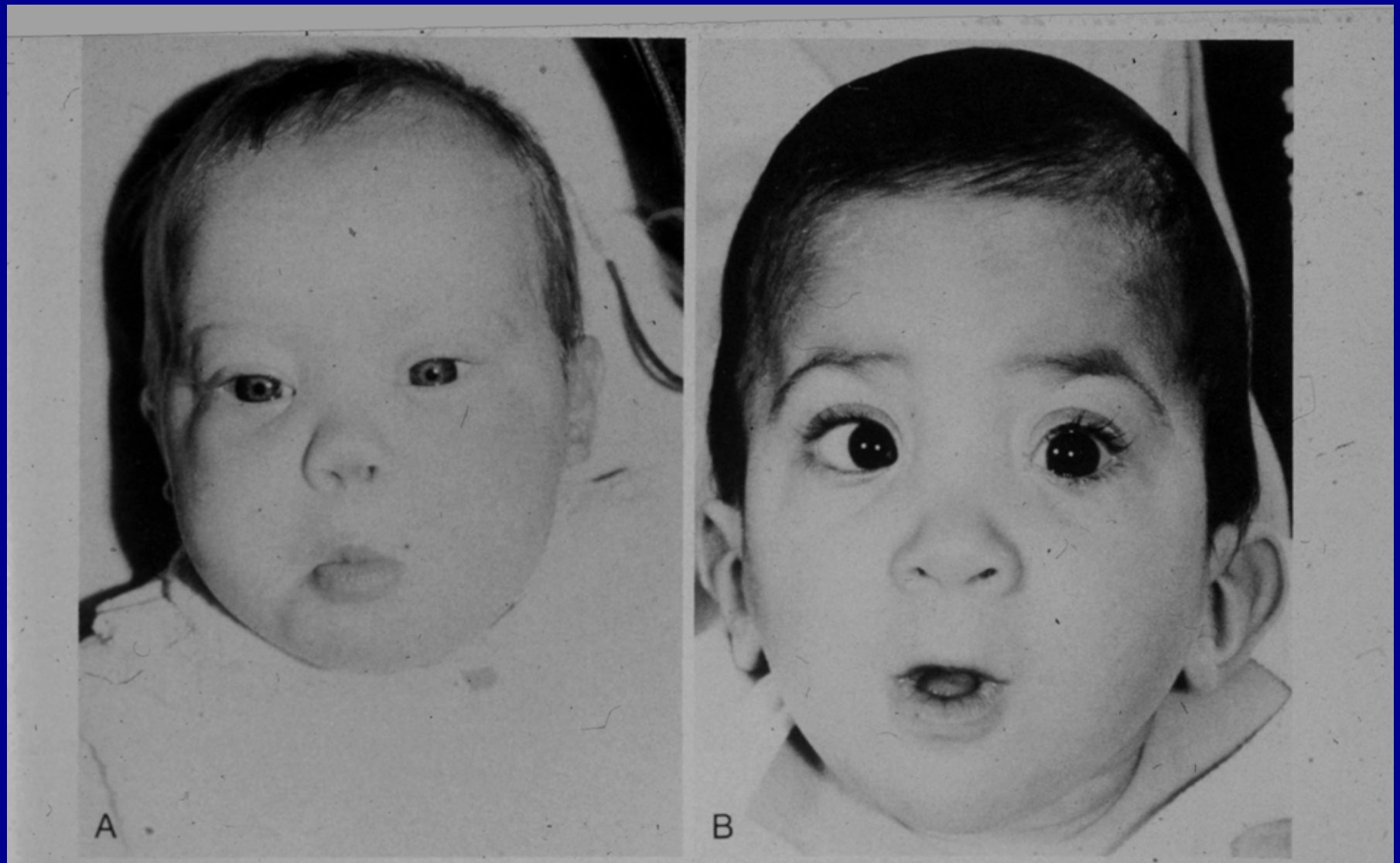
Arch Neurol. 2009;66(8):979-984

Fetal Antiepileptic Exposure

- growth retardation
- microcephaly
- craniofacial dysmorphy
- mental retardation
- cleft lip / palate
- hypoplasia of distal phalanx

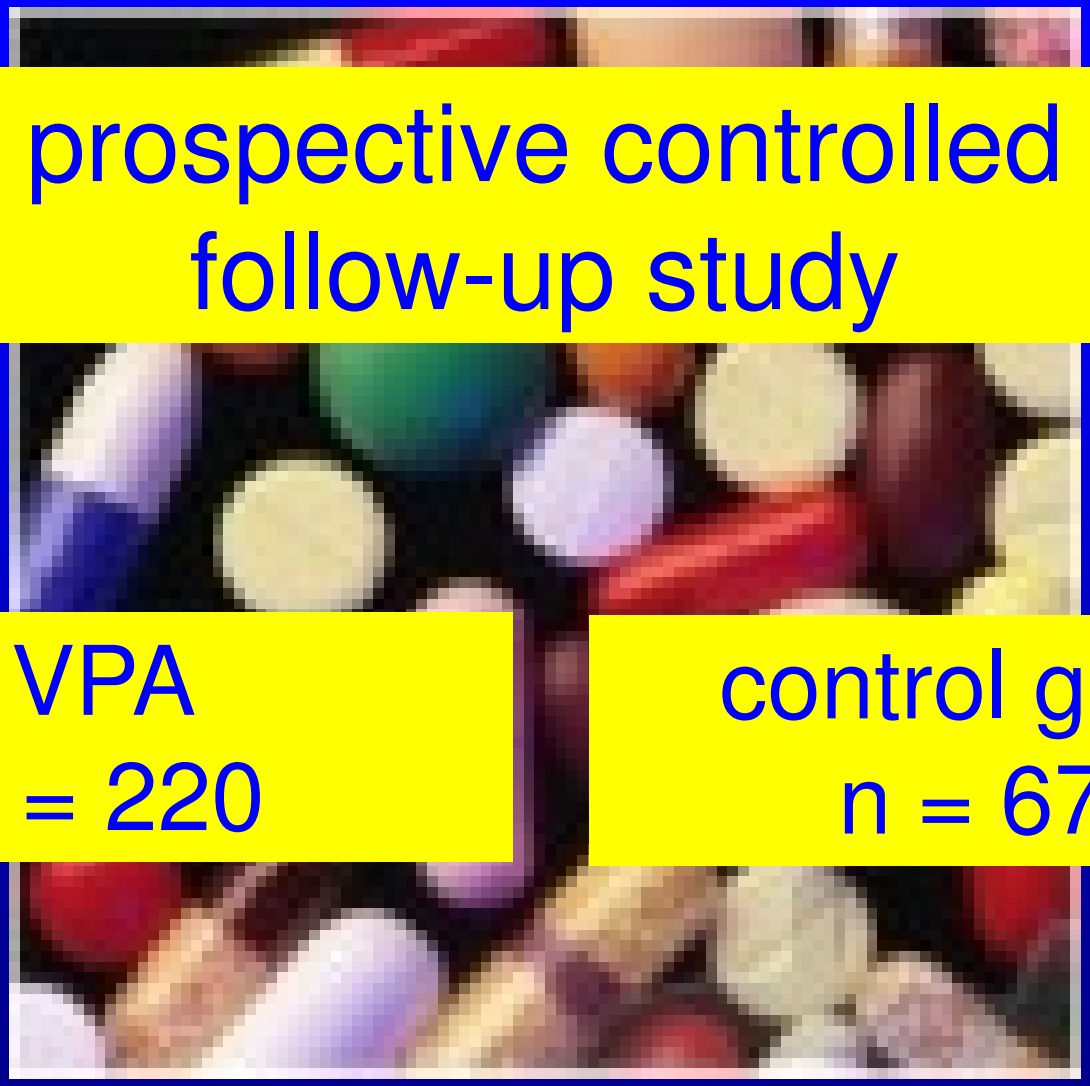
Valproic Acid - Anomalies

- midfacial hypoplasia, prominent forehead
- congenital heart disease
- limb reduction defects
- decreased postnatal growth
- lumbosacral spina bifida: 1 to 2%



Fetal valproate effects. *A*, Seven month old girl with epicanthal folds that connect with an infraorbital crease, short nose, long philtrum, and small mouth. *B*, Ten month old boy with a short nose, long philtrum with a thin vermillion border, and a relatively small mouth. (From Diliberti, J. H., et al.: Am. J. Med. Genet., *19*:473, 1984.)

Study Design



prospective controlled
follow-up study

VPA
n = 220

control group
n = 679

Valproic Acid
- elective termination of pregnancy (ETOP) -

	ETOP	No ETOP	total
VPA	30 **13.6%**	190 **86.4%**	220 **100.0 %**
Control	18 **2.7%**	661 **97.3%**	679 **100.0 %**

Fisher´s Exact Test: $p < 0.001$

Valproic Acid
- fetal loss -

	fetal loss	birth	total
VPA	19 **10.0%**	171 **90.0%**	190 **100.0%**
control	77 **11.7%**	584 **88.3%**	661 **100.0%**

Fisher´s Exact Test: n.s.

Valproic Acid
- congenital anomalies -

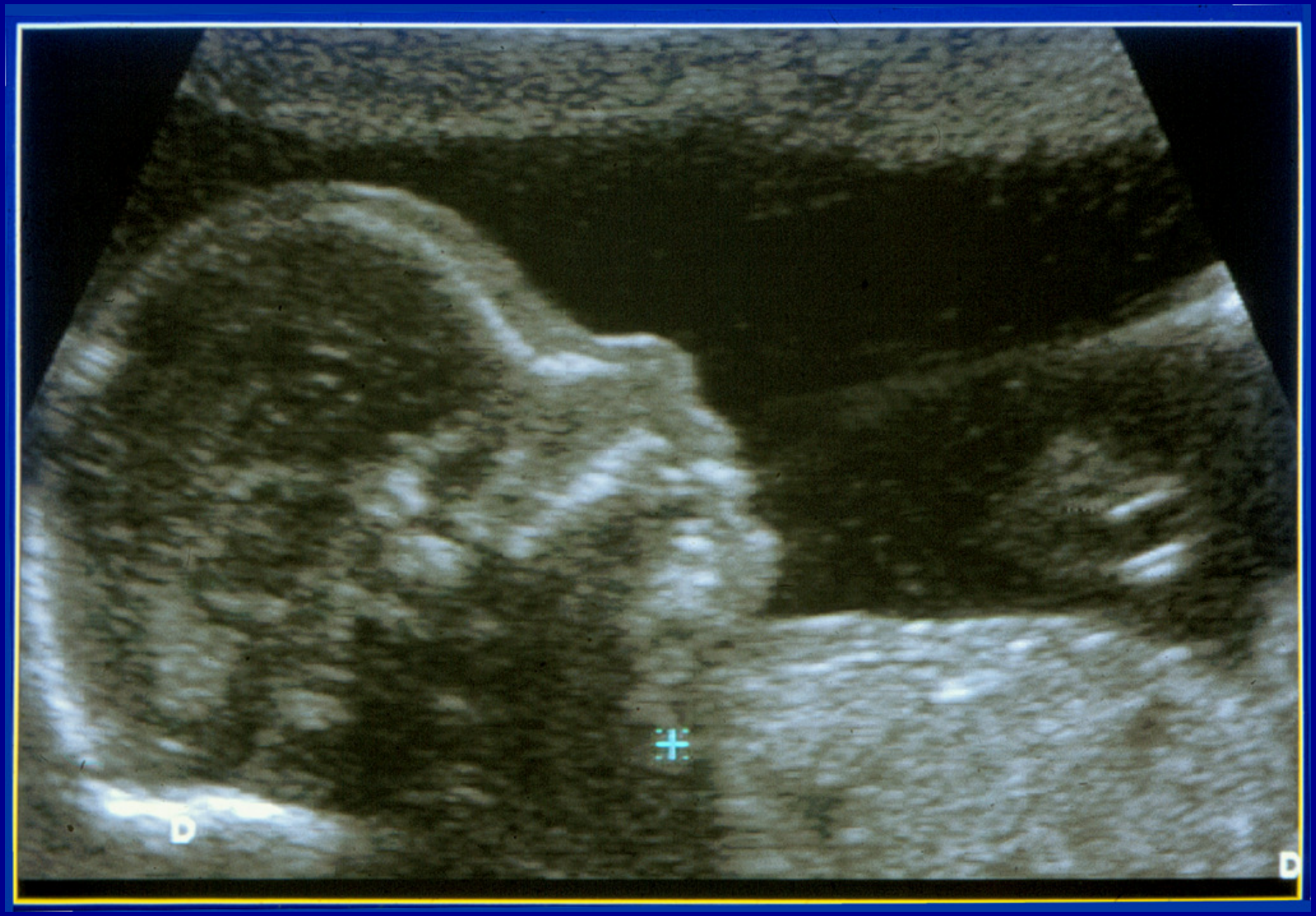
	congenital anomaly	healthy baby	total
VPA	27 **15.8%**	144 **84.2%**	171 **100.0%**
control	26 **4.5%**	558 **95.5%**	584 **100.0%**

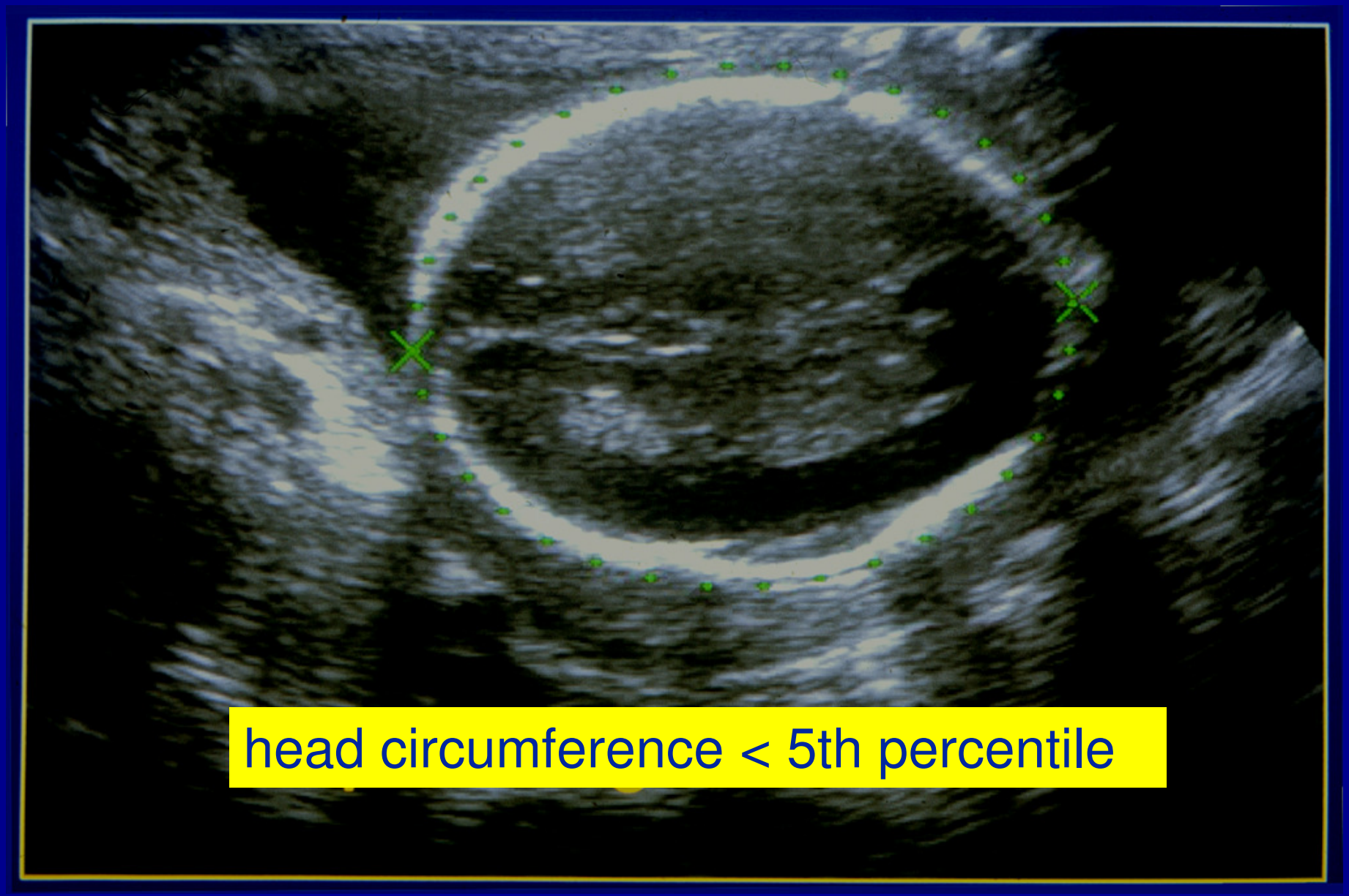
Fisher´s Exact Test: $p < 0.0001$

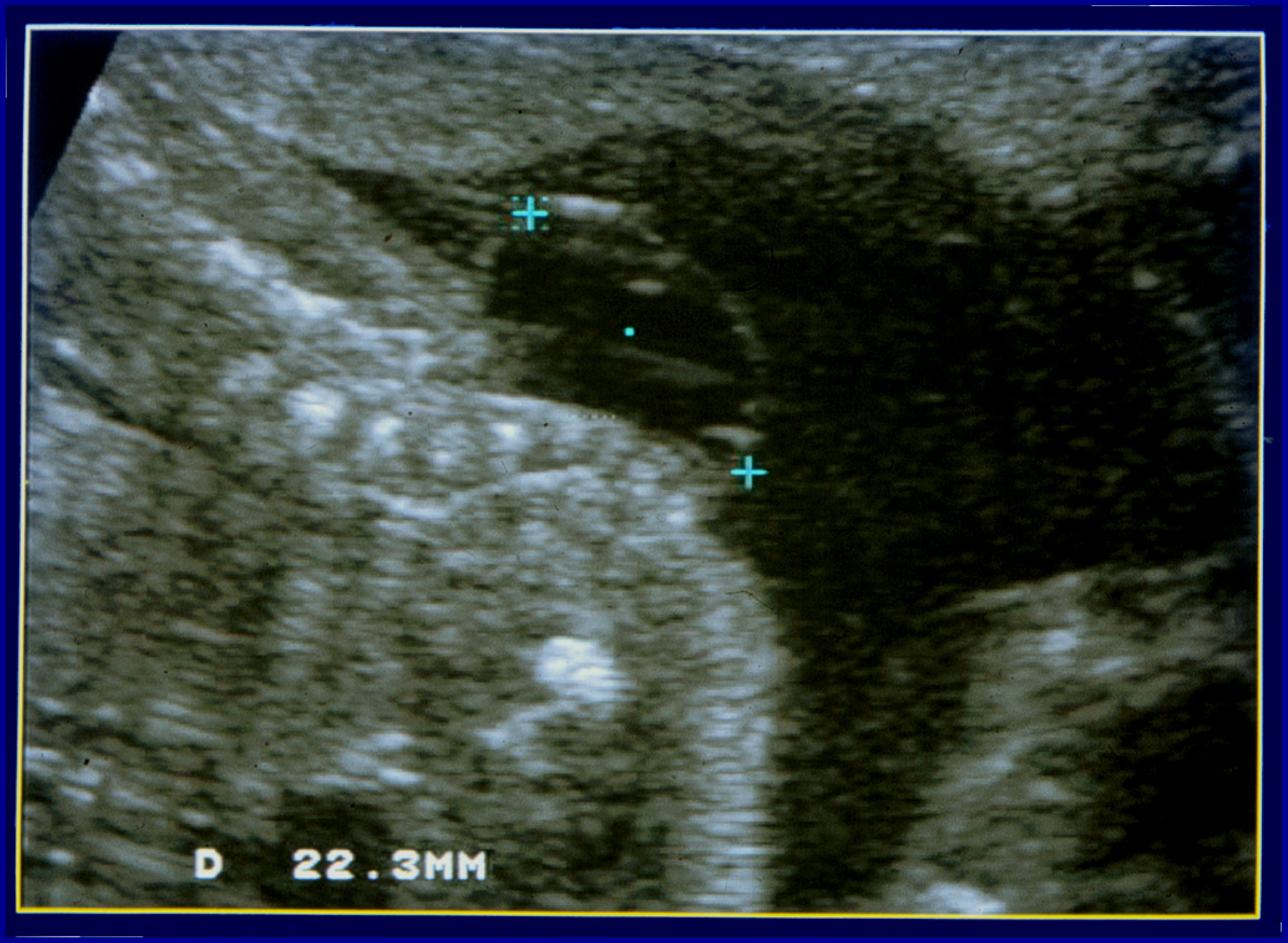
Congenital Anomalies after Exposure to VPA in Early Pregnancy

relative risk = 3.3

(95% confidence interval: 1.7, 6.1)




head circumference < 5th percentile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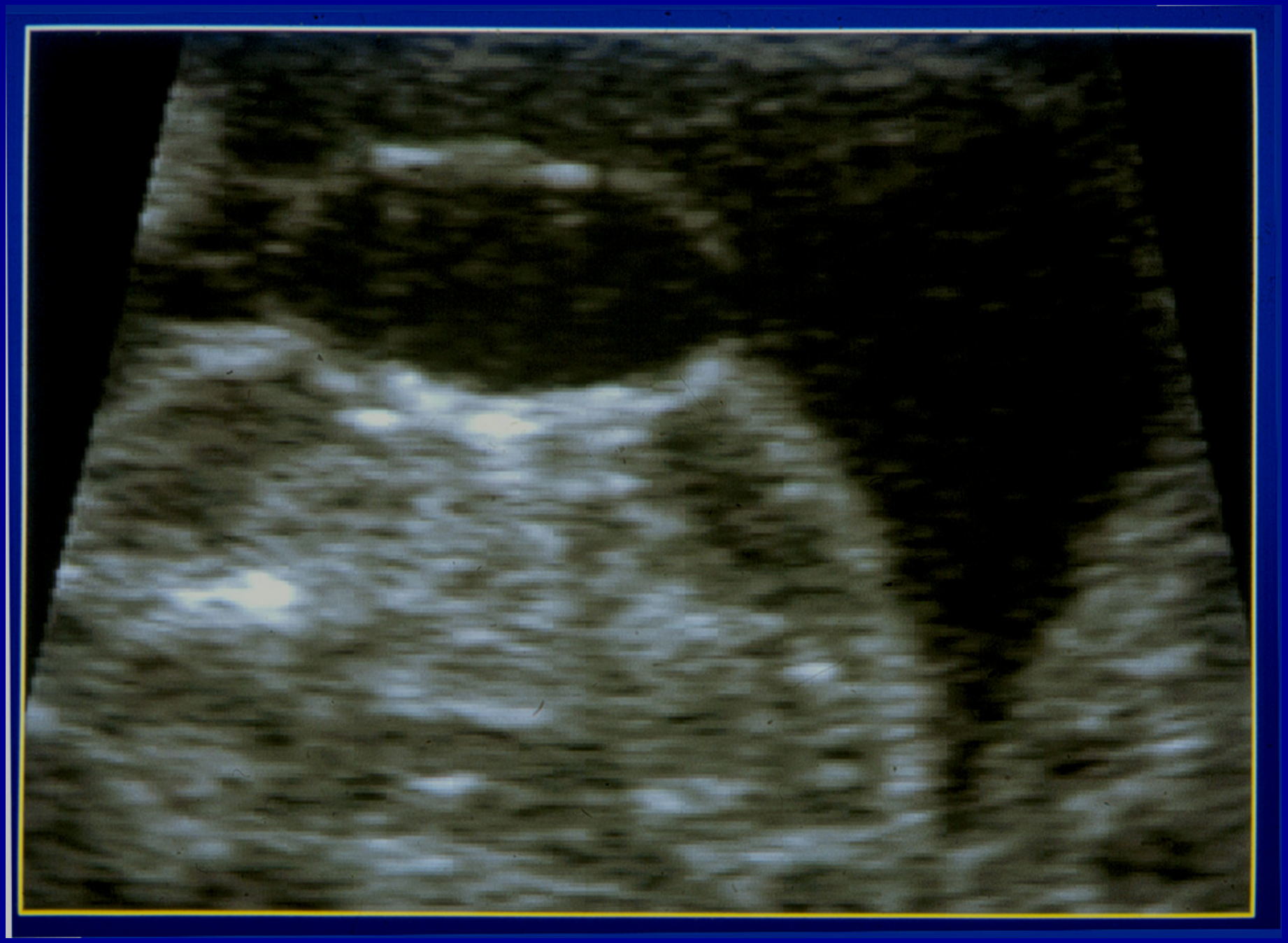
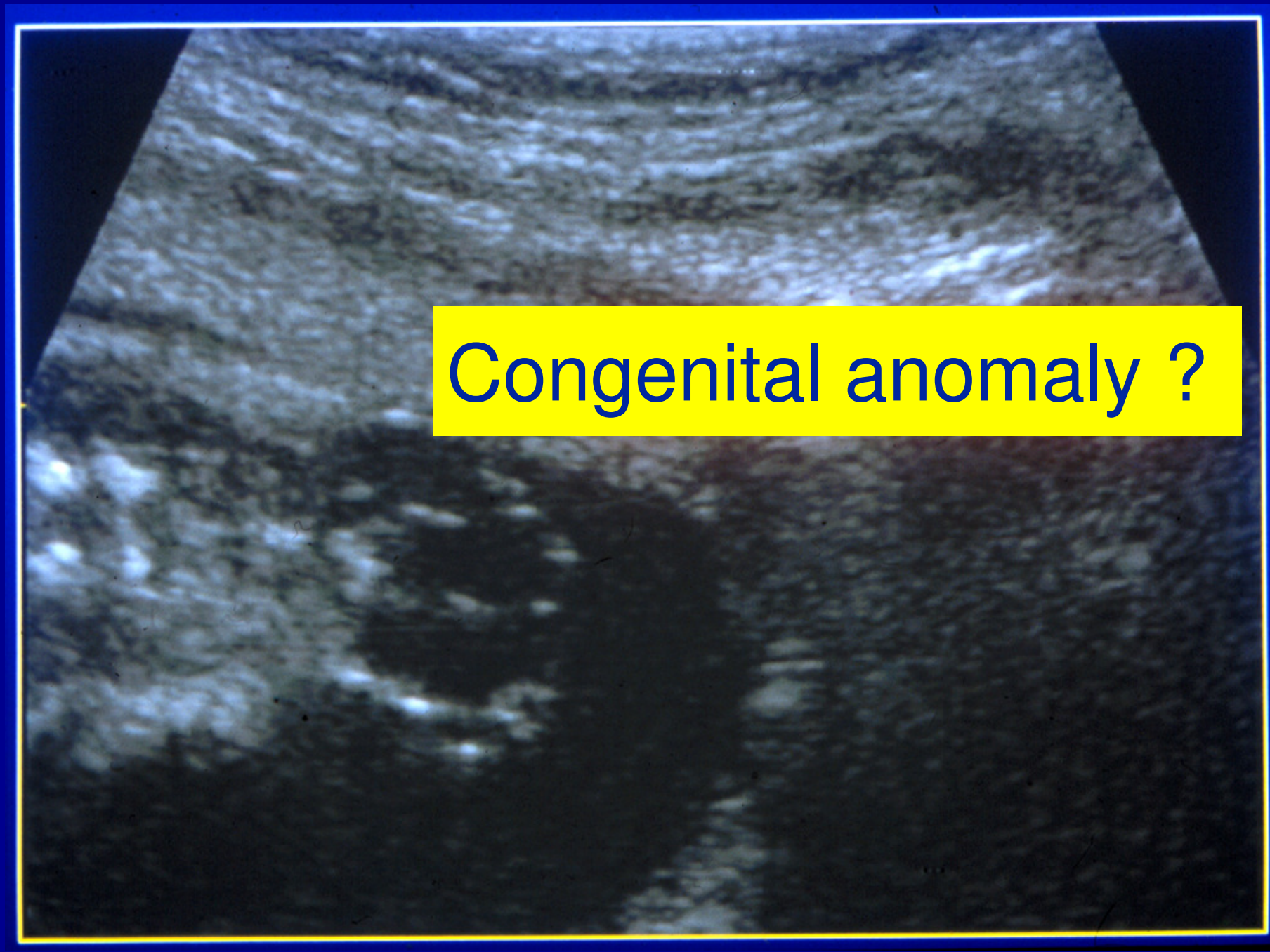
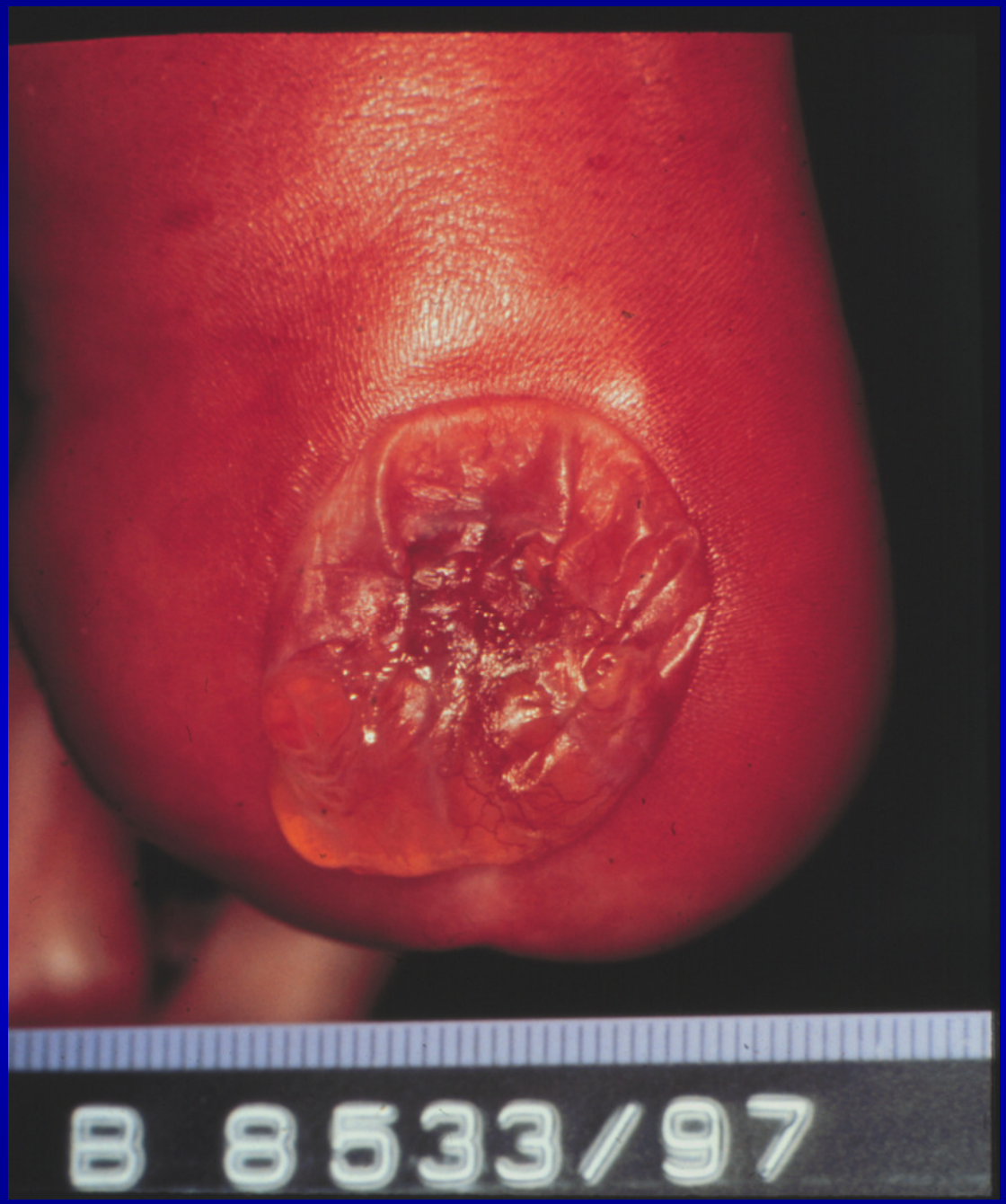
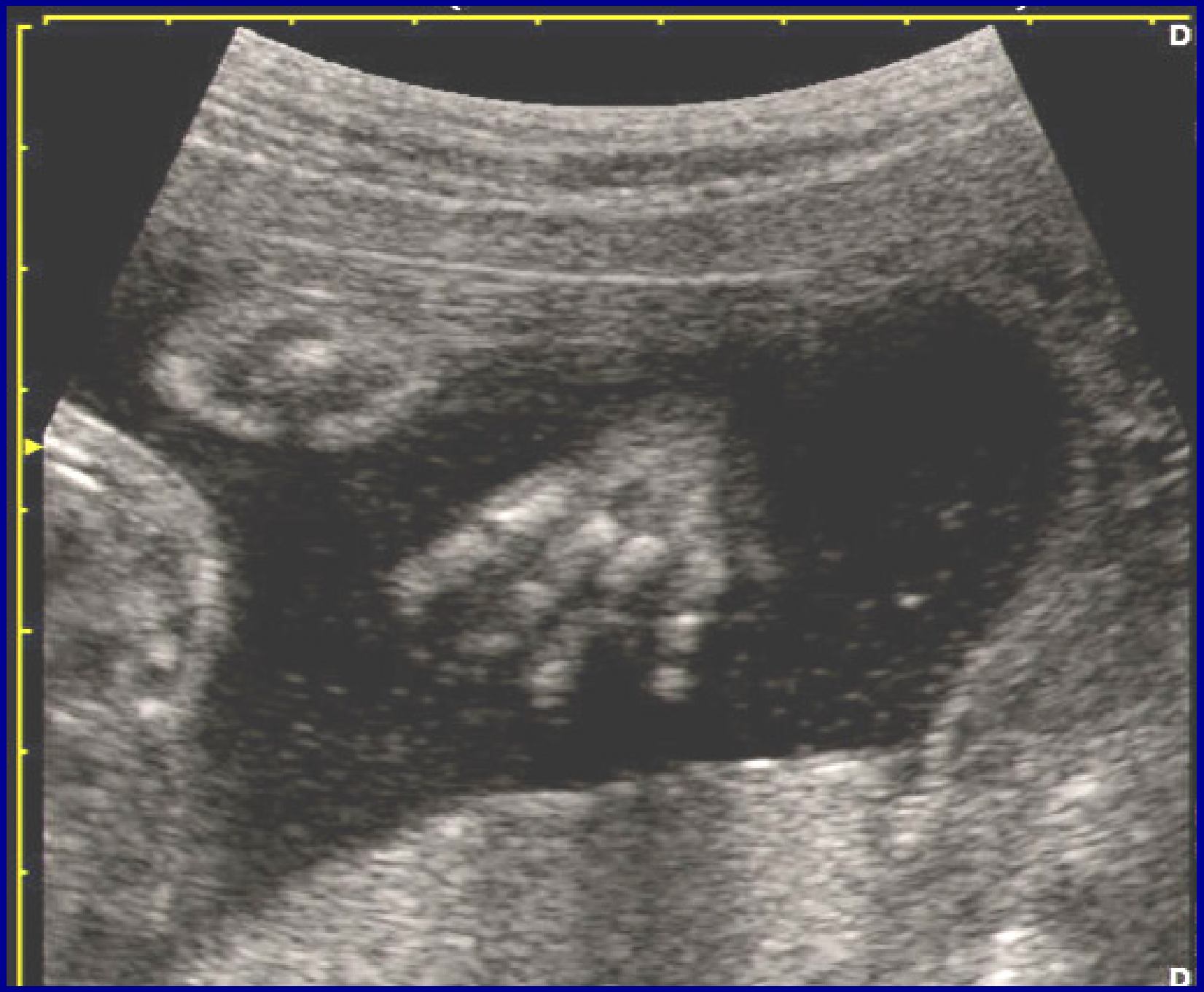



Congenital anomaly ?


B 8533/97

Valproate Embryopathy maternal medication

- VPA 2700 mg/d
- Phenobarbital 175 mg/d
- Mesuximide 600 mg/d
- Sertraline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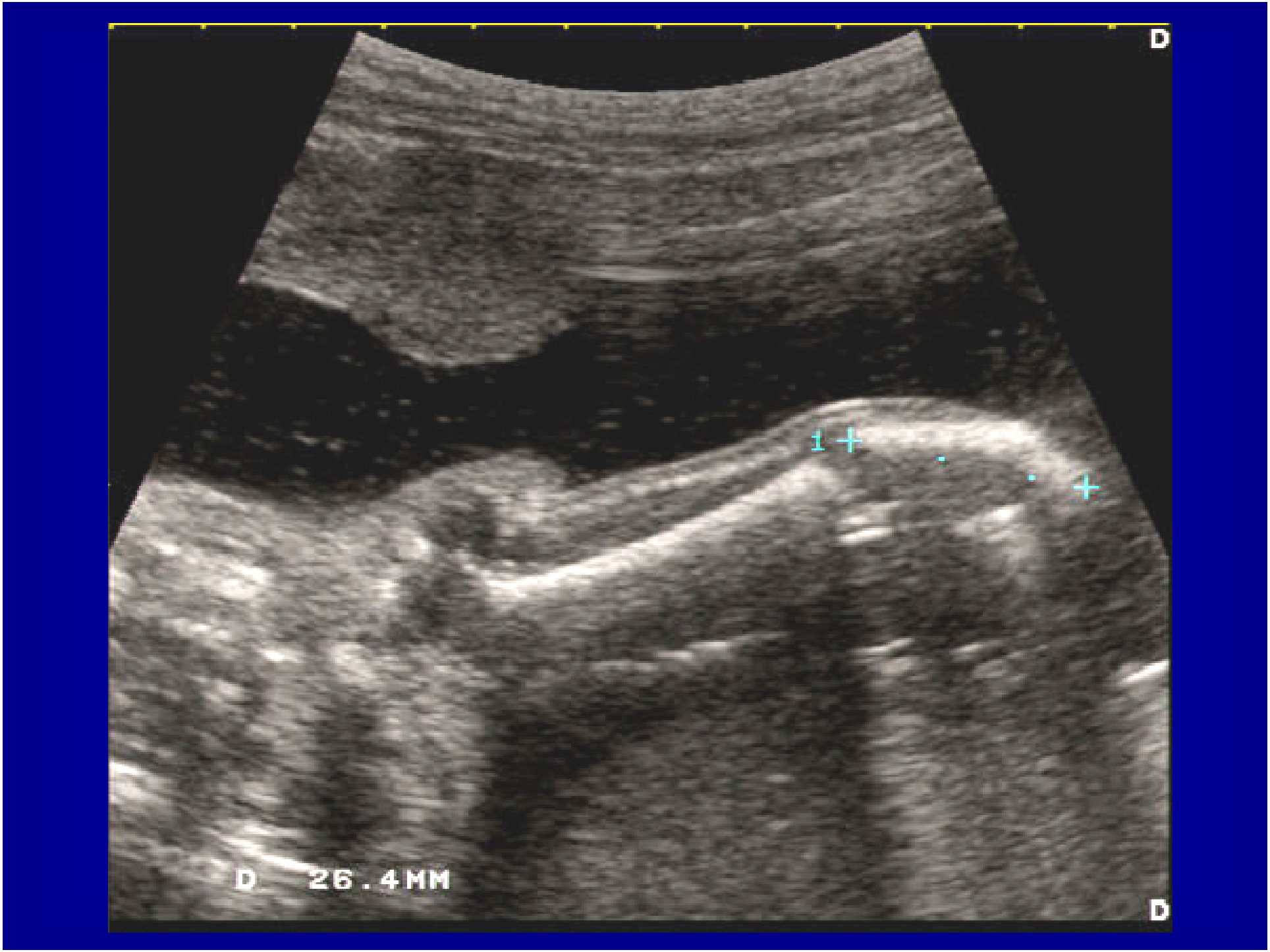
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D 26.4MM
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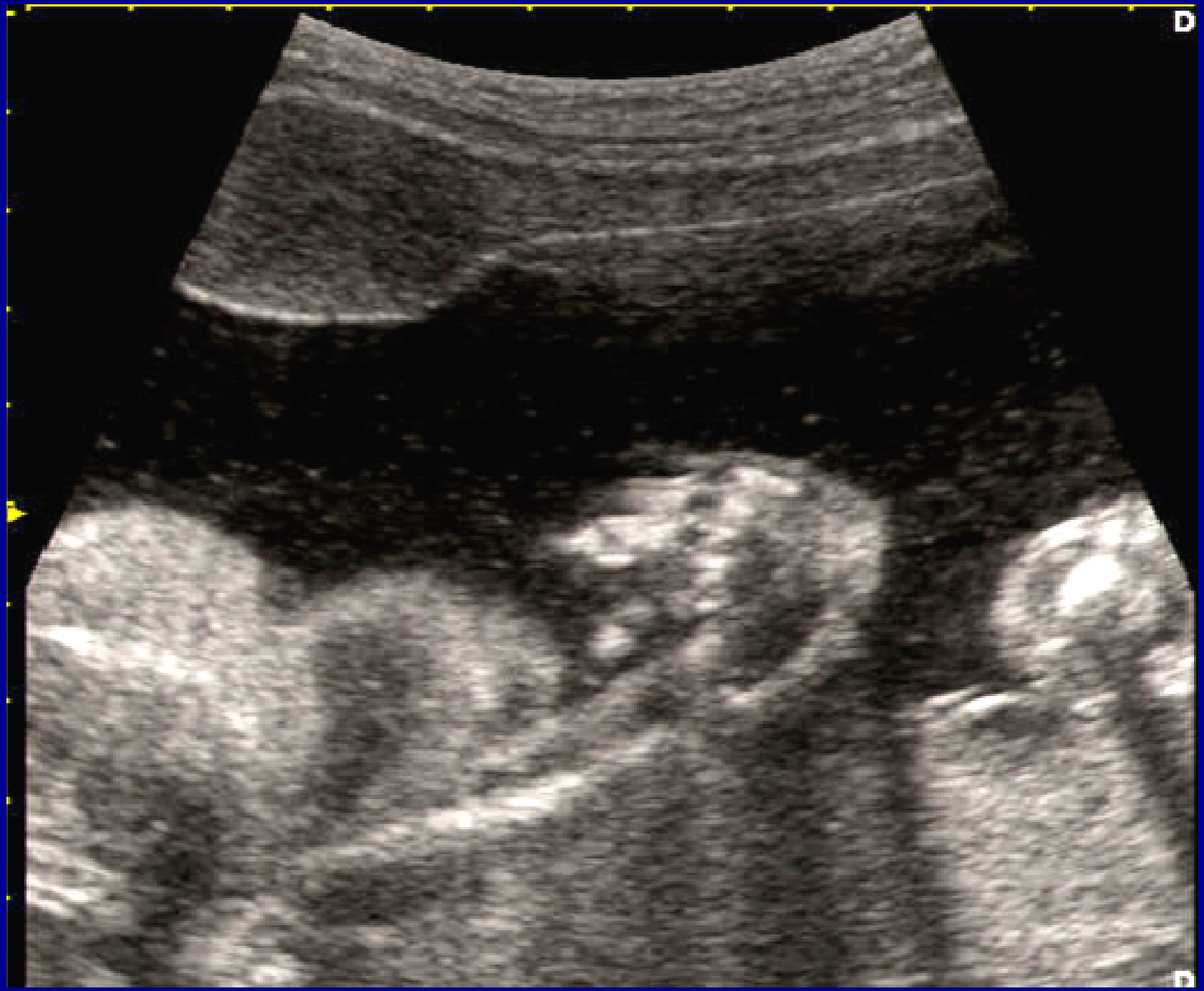
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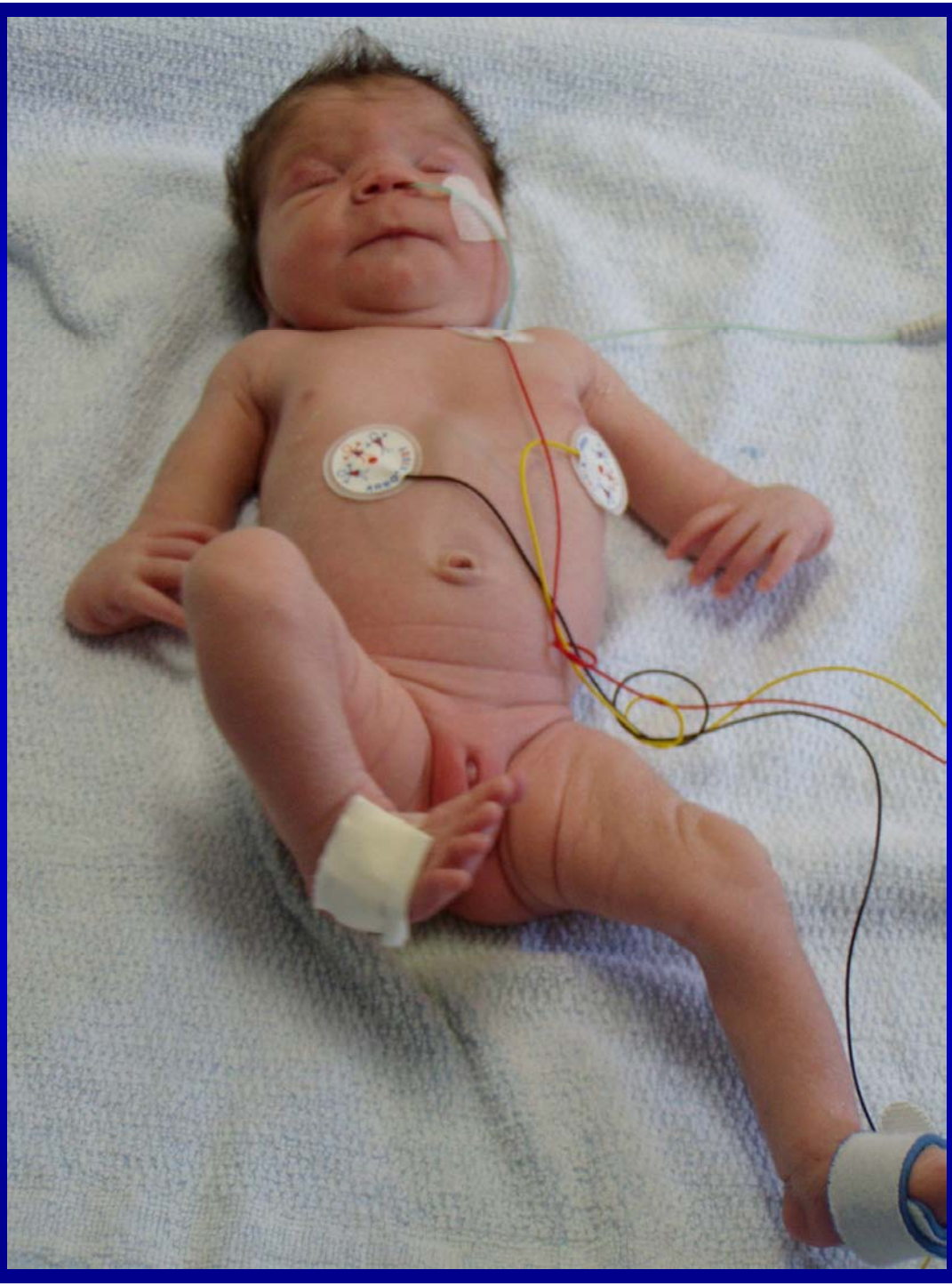
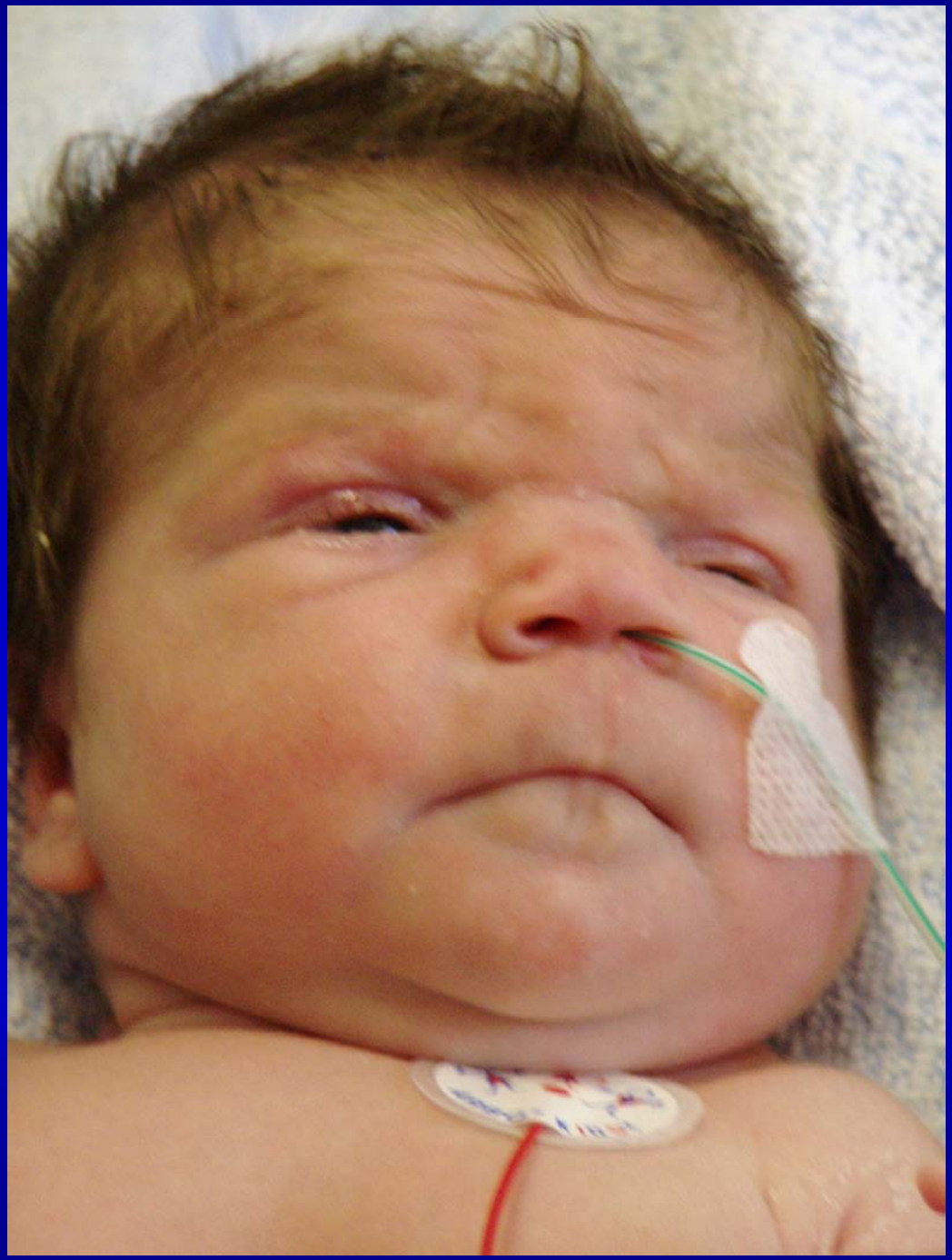
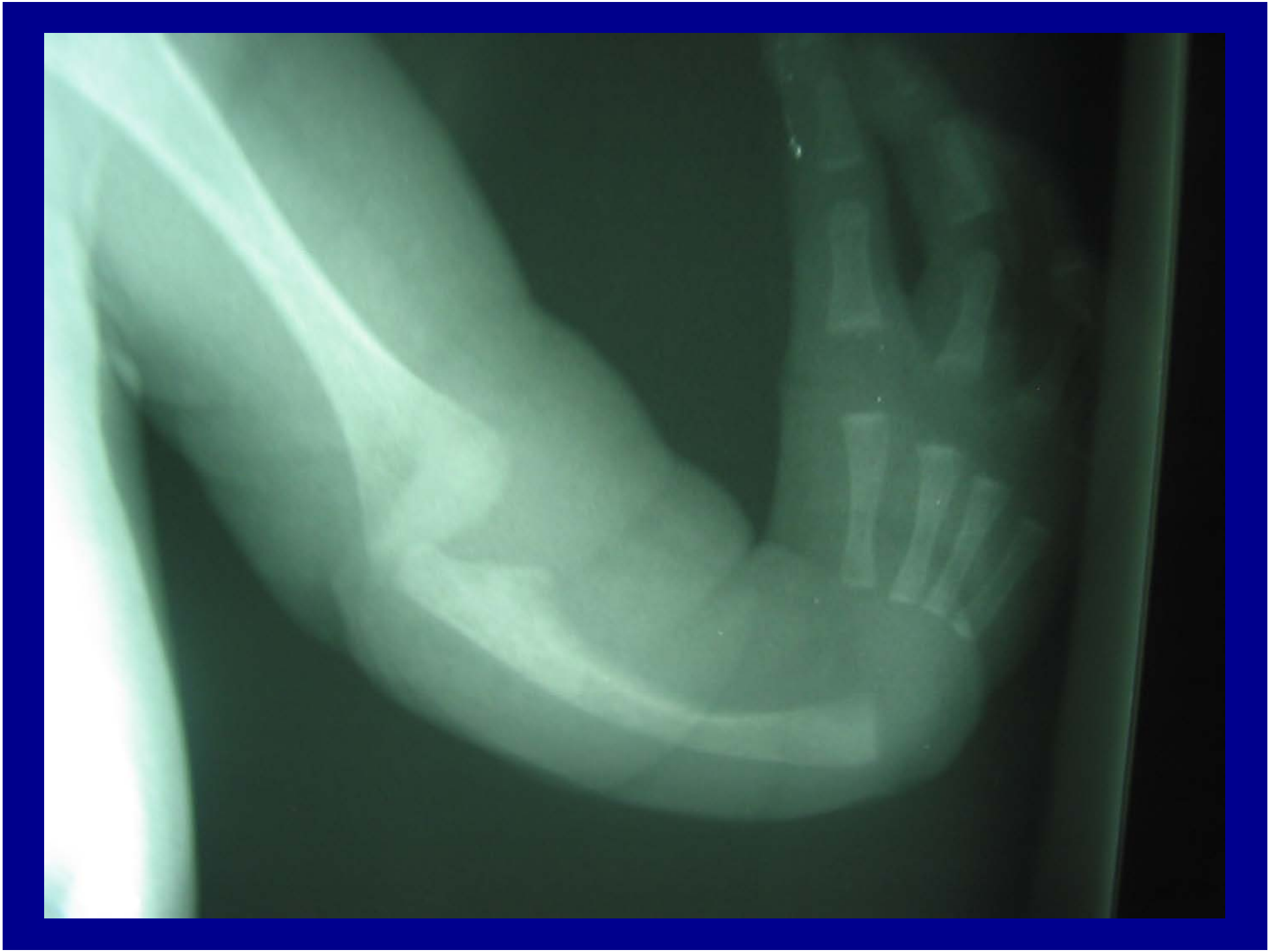






Cognitive abilities and behaviour of children exposed to antiepileptic drugs *in utero*

Rebecca L. Bromley[a], Gus A. Baker[a] and Kimford J. Meador[b]

Recent evidence from large prospective cohorts indicates that there is a long term risk to the cognitive and behavioural development of the child exposed in utero to sodium valproate.

Information on other antiepileptic agents is conflicting or nonexistent and more research in this area is urgently required.

Current Opinion in Neurology 2009, 22:162–166

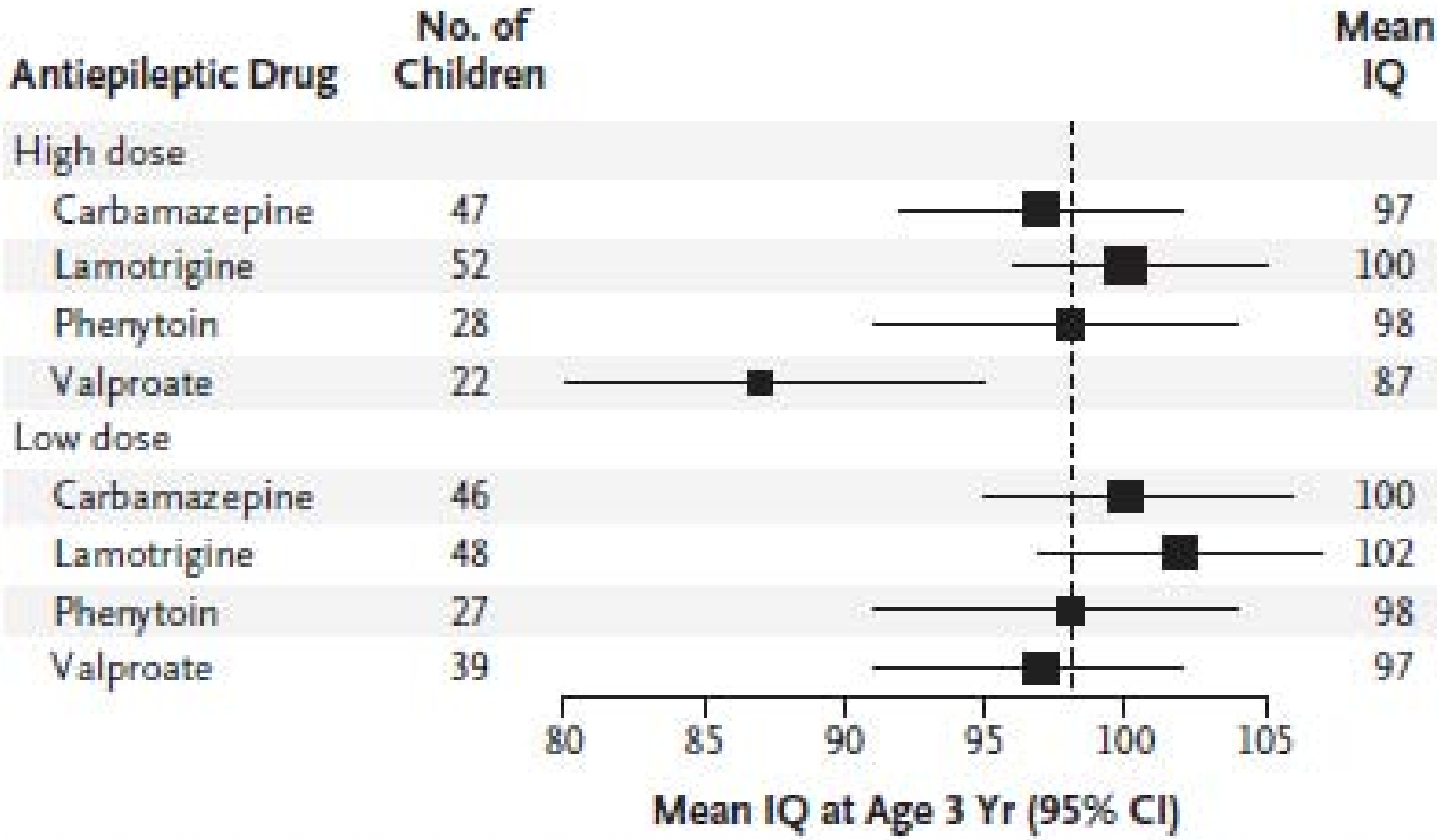


Figure 1. IQ Scores of Children Who Were Exposed to Antiepileptic Drugs In Utero, According to Drug and Dose.

Meador et al. N Engl J Med. 2009;360(16):1597-605

Cognitive and behavioural impact of exposure to valproic acid in utero

- autistic spectrum disorders
- lower verbal IQ
- lower level of intellectual functioning (IQ < 70)
- lower score in attentional and memory tasks

Bromley et al. Current Opinion in Neurology 2009;22:162–166

The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists☆,☆☆

Kimberly A. Yonkers, M.D.[a,b,*], Katherine L. Wisner, M.D., MS.[c,d], Donna E. Stewart, M.D., FRCPC[e], Tim F. Oberlander, M.D., FRCPC[f], Diana L. Dell, M.D., FACOG[g], Nada Stotland, M.D., M.P.H.[h,i], Susan Ramin, M.D., FACOG[j], Linda Chaudron, M.D., MS.[k], Charles Lockwood, M.D., FACOG[l]

14% - 23% of pregnant women experience depressive symptoms during pregnancy

13% of women who were pregnant in 2003 were treated with an antidepressant

OBSTETRICS & GYNECOLOGY VOL. 114, NO. 3, SEPTEMBER 2009

Maternal risks of untreated depression

- decreased nutrition
- disrupted sleep
- difficulties in following medical recommendations
- risk of suicide
- increased exposure to tobacco, alcohol and drugs

Fetal risks of untreated depression

- fetal growth retardation, low birth weight
- smaller head circumference
- preterm birth
- operative delivery
- lower Apgar scores
- altered mother–infant bonding
- mental retardation
- increased morbidity and mortality of the newborn

FDA Alert for Healthcare Professionals

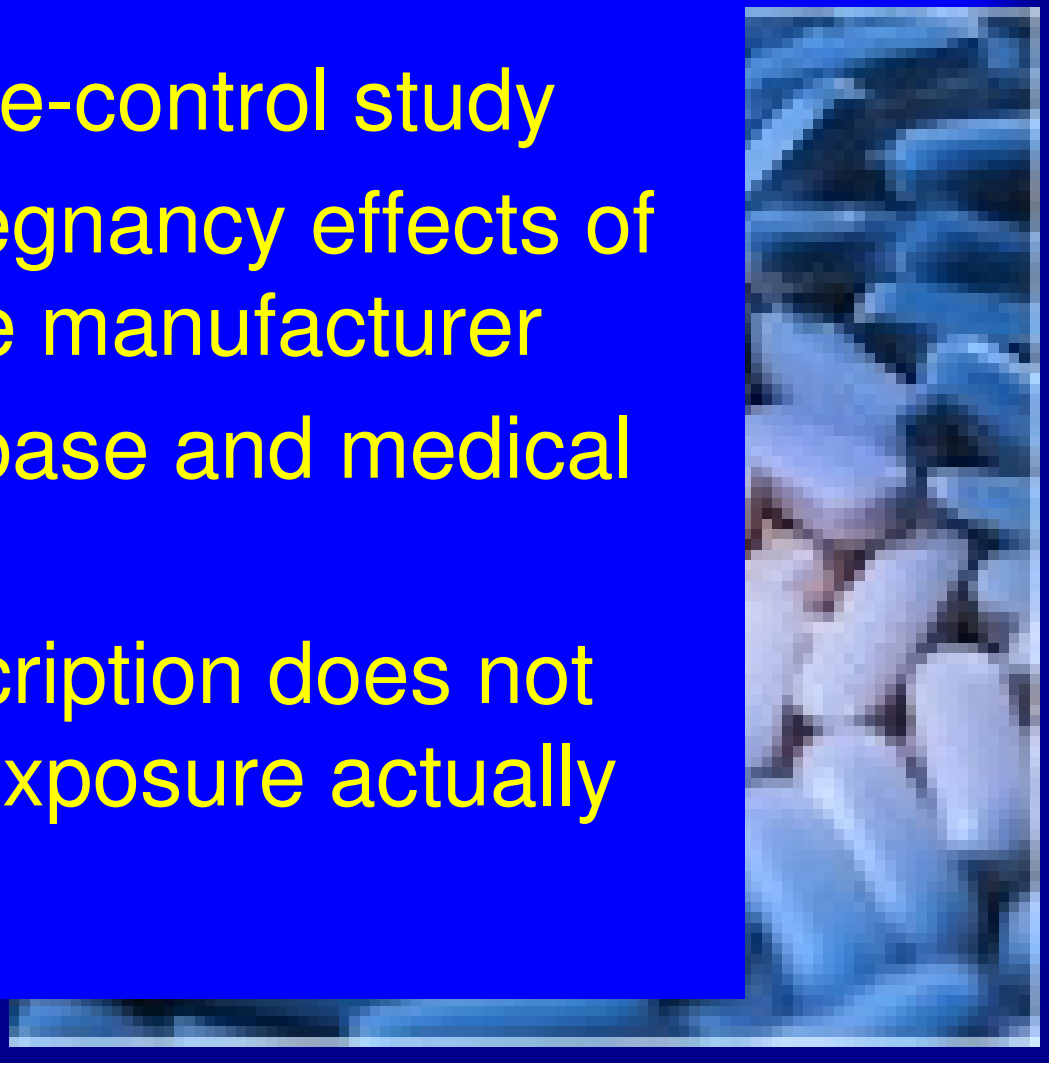
Paroxetine hydrochloride (marketed as Paxil)

FDA ALERT [12/2005]: Increase in the Risk of Birth Defects

The FDA has determined that exposure to paroxetine in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations.

GSK: Updated Preliminary Report on Bupropion and Other Antidepressants

- unpublished case-control study
- evaluation of pregnancy effects of bupropion by the manufacturer
- insurance data base and medical record review
- paroxetine prescription does not guarantee that exposure actually occurred



Paroxetine - Animal Pregnancy Testing

Rabbits given up to 5.1 mg/kg/d

no increase in offspring anomalies

Rats given up to up to 43 mg/kg/d

Evaluation of the risk of Congenital Cardiovascular Defects Associated With Use of Paroxetine During Pregnancy

Adrienne Einarson, R.N.

Alessandra Pistelli, M.D., Ph.D.

Marco DeSantis, M.D.

Heli Malm, M.D.

Wolfgang D. Paulus, M.D.

Alice Panchaud, Ph.D.

Debra Kennedy, M.D.

Thomas R. Einarson, Ph.D.

Gideon Koren, M.D.

Objective: In 2005–2006, several studies noted an increased risk of cardiovascular birth defects associated with maternal use of paroxetine compared with other antidepressants in the same class. In this study, the authors sought to determine whether paroxetine was associated with an increased risk of cardiovascular defects in infants of women exposed to the drug during the first trimester of pregnancy.

Method: From teratology information services around the world, the authors collected prospectively ascertained, unpublished cases of infants exposed to paroxetine early in the first trimester of pregnancy and compared them with an unexposed cohort. The authors also contacted the authors of published database studies on antidepressants as a class to determine how many of the women in those studies had been exposed to paroxetine and the rates of cardiovascular defects in their infants.

Results: The authors were able to ascertain the outcomes of 1,174 infants from eight services. The rates of cardiac defects in the paroxetine group and in the unexposed group were both 0.7%. The rate in the database studies (2,061 cases from four studies) was 1.5%.

Conclusions: Paroxetine does not appear to be associated with an increased risk of cardiovascular defects following use in early pregnancy, as the incidence in more than 3,000 infants was well within the population incidence of approximately 1%.

(Am J Psychiatry Einarson et al.; AiA:1–5)

Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis

Emilio J Sanz, Carlos De-las-Cuevas, Anne Kiuru, Andrew Bate, Ralph Edwards

Summary

Background Selective serotonin reuptake inhibitors (SSRIs) have been associated with withdrawal symptoms. We investigated whether use of these drugs in pregnant women might cause neonatal withdrawal syndrome.

Methods An association between paroxetine and neonatal convulsions was identified in December, 2001, by the data mining method routinely used to screen the WHO database of adverse drug reactions. An information component (IC) measure was used to screen for unexpected adverse reactions relative to the information in the database. We then assessed cases of neonatal convulsions and neonatal withdrawal syndrome associated with drugs included in the anatomical therapeutic chemical groups N06AB and N06AX.

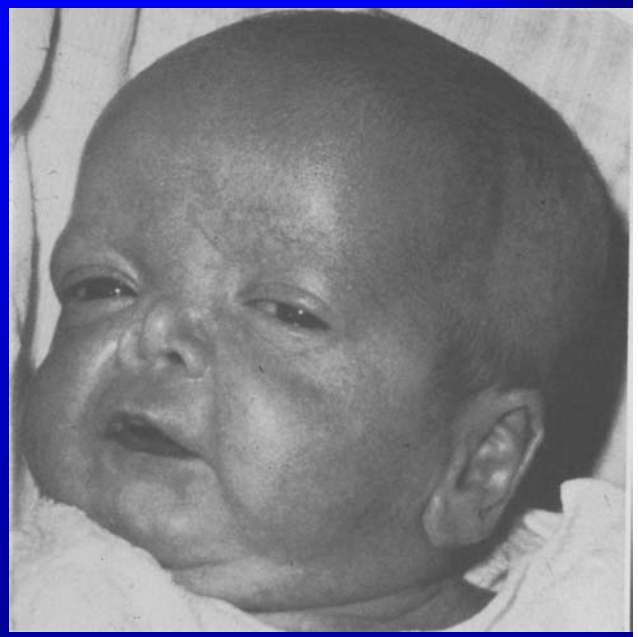
Findings By November, 2003, a total of 93 suspected cases of SSRI-induced neonatal withdrawal syndrome had been reported, and were regarded as enough information to confirm a possible causal relation. 64 of the cases were associated with paroxetine, 14 with fluoxetine, nine with sertraline, and seven with citalopram. The IC–2 SD for the group became greater than 0 in the first quarter of 1991, and the IC increased to 2·68 (IC–2 SD 0·32) by the second quarter of 2003. For each individual compound, the IC–2 SD was greater than 0.

Interpretation SSRIs, especially paroxetine, should be cautiously managed in the treatment of pregnant women with a psychiatric disorder.

Lancet 2005; 365: 482–87

Fetal Warfarin Syndrom

- mid face hypoplasia
- defects in calcification of the epiphises (chondrodysplasia punctata)
- microphthalmia, blindness
- hearing loss
- growth retardation
- CNS defects, mental retardation
- heart defects, anomalies of the urinary tract?

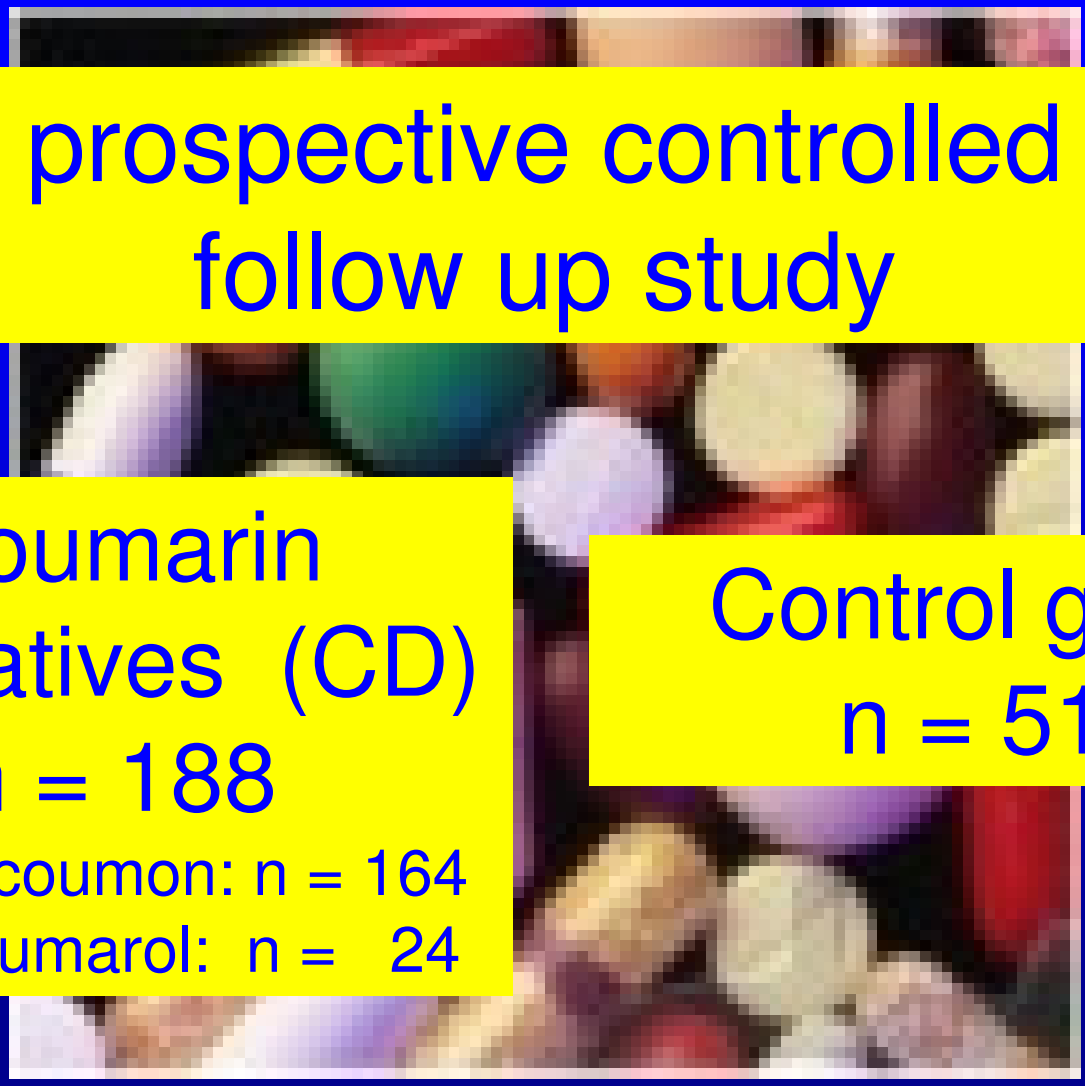


Phenprocoumon

„Conception has to be avoided during medication with phenprocoumon and in a peroid of 3 months after discontinuation of the therapy because of teratogenic risks."

Rote Liste 2009, Marcumar®

Study Design



prospective controlled
follow up study

Coumarin
Derivatives (CD)
n = 188

- Phenprocoumon: n = 164
- Acenocoumarol: n = 24

Control group
n = 517

Coumarin Derivatives (CD)
- elective termination of pregnancy (ETOP) -

	ETOP	No ETOP	total
CD	71 **37.8%**	117 **62.2%**	188 **100.0%**
Control	17 **3.3%**	500 **96.7%**	517 **100.0%**

Fisher´s Exact Test: $p < 0.001$

Coumarin Derivatives (CD)
- fetal loss -

	fetal loss	birth	total
CD	36 **30.1 %**	81 **69.9 %**	117 **100.0 %**
control	70 **14.0%**	430 **86.0 %**	500 **100.0 %**

Fisher´s Exact Test: $p < 0.001$

Coumarin Derivatives (CD)
- congenital anomalies -

	congenital anomaly	healthy baby	Total
CD	11 **13.6%**	70 **86.4%**	81 **100.0%**
control	21 **4.9%**	409 **95.1%**	430 **100.0%**

Fisher´s Exact Test: p = 0,009

period of exposure
- congenital anomalies -

	congenital anomaly	healthy baby	total
wk 8/0	3 **4.6 %**	62 **95.4 %**	65 **100.0 %**
> wk 8/0	7 **43.4 %**	9 **56.6 %**	16 **100.0 %**

Fisher´s Exact Test: $p < 0{,}001$

congenital anomalies after exposure to coumarin derivatives > wk 8

relative risk = 9.48

(95% confidence interval 2.48 – 43.10)

Vitamin K antagonists and pregnancy outcome

A multi-centre prospective study

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The risk for coumarin embryopathy is, however, very small, in particular when therapy during the 1st trimester did not take place later than week 8 after the 1st day of the last menstrual period.

Thromb Haemost 2006; 95: 949–57

We need

- large prospective controlled follow up studies
- long term follow up

in order to evaluate the impact oft maternal substance use on childhood outcome.


Thank you very much for your attention!