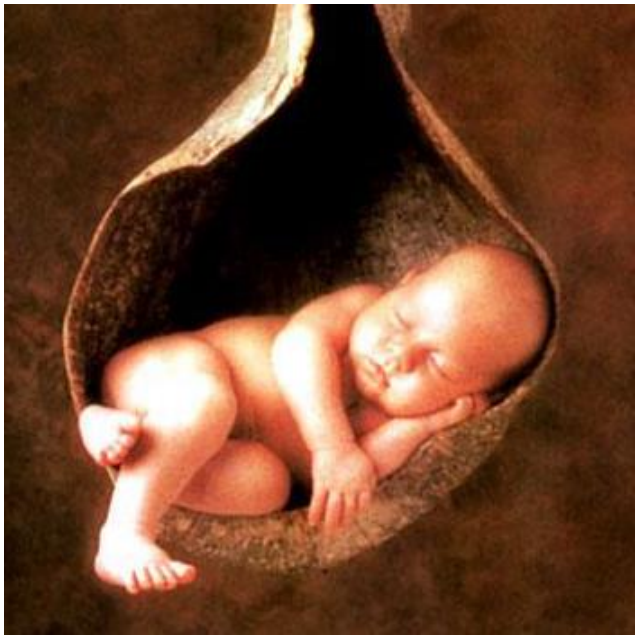


Medicines use in pregnancy and lactation

Prof. dr. Jolanta Gulbinovič

The use of the prescription medicines during pregnancy in Norway

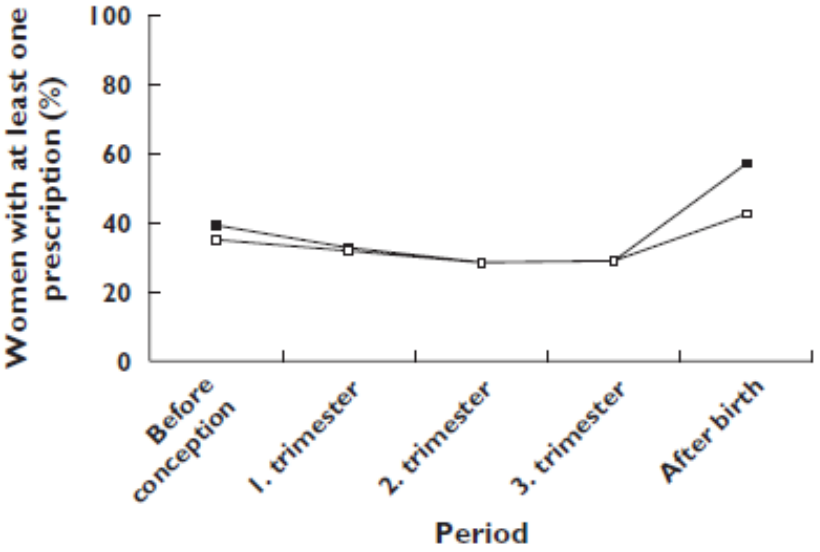


Figure 1

Percentage of mothers who had dispensed prescriptions 3 months prior to pregnancy to 3 months after pregnancy (based on $n = 106\,329$ pregnancies). (All drugs, (■); Excl. Contraceptives, (□))

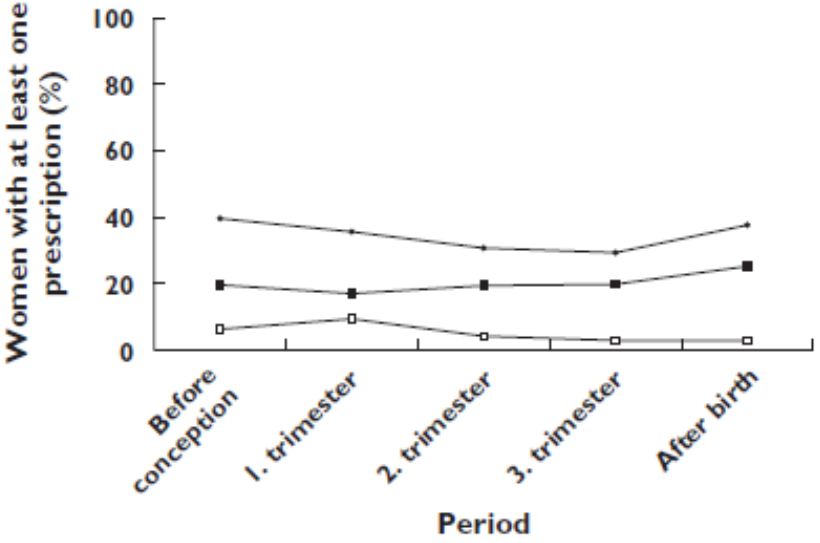


Figure 2

Percentage of women who had dispensed prescriptions for three categories of drugs, defined by Bakker *et al.* [4], from 3 months prior to pregnancy to 3 months after pregnancy (based on $n = 106\,329$ pregnancies). (Drugs for chronic conditions, (■); Drugs for occasional and short-time use, (□); Pregnancy-related drugs, (●))

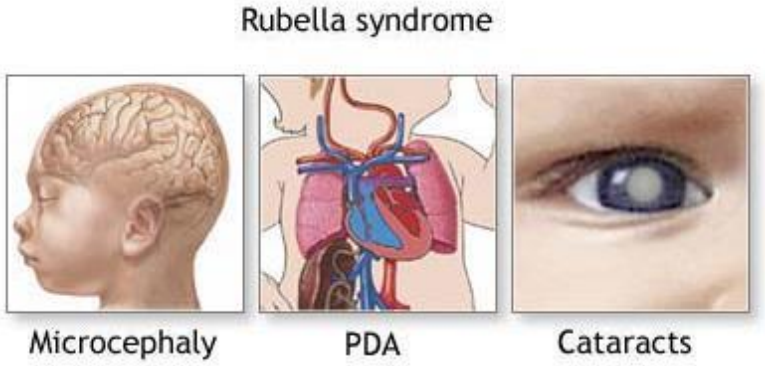
Br J Clin Pharmacol / **65**:5 / 653–660

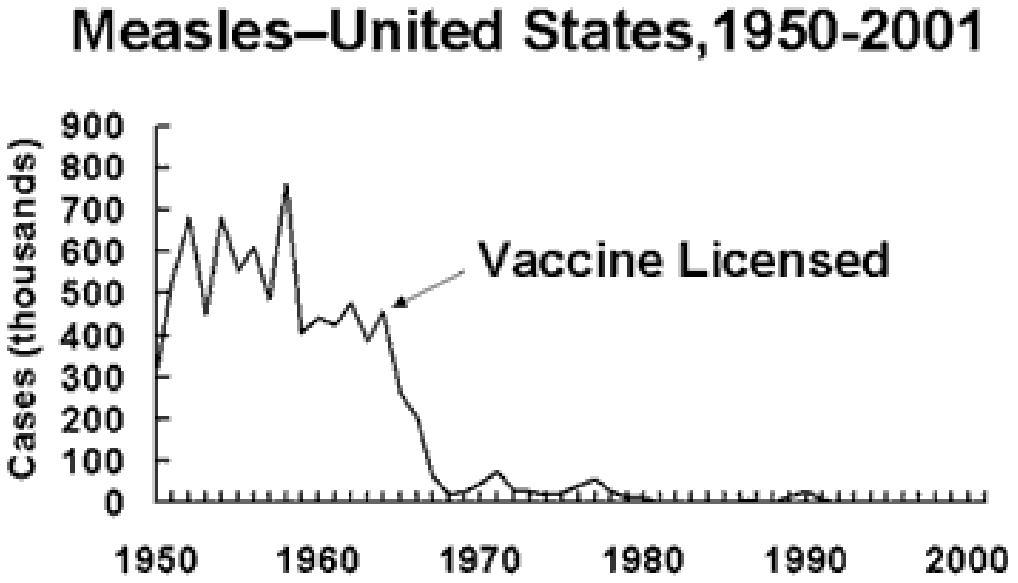
Historical perspective

- Rubella induced malformations
- Thalidomide catastrophe
- Bendectin (doxylamine + pyridoxine) story
- Chernobyl catastrophe

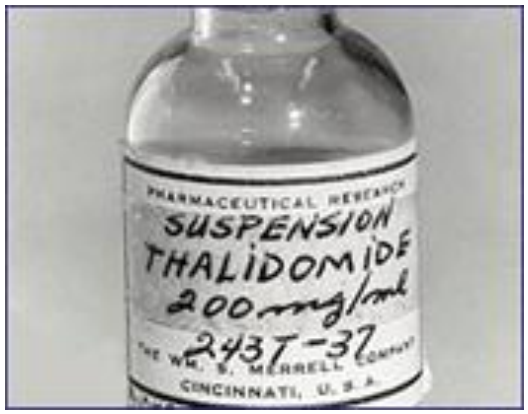
Intrauterine rubella

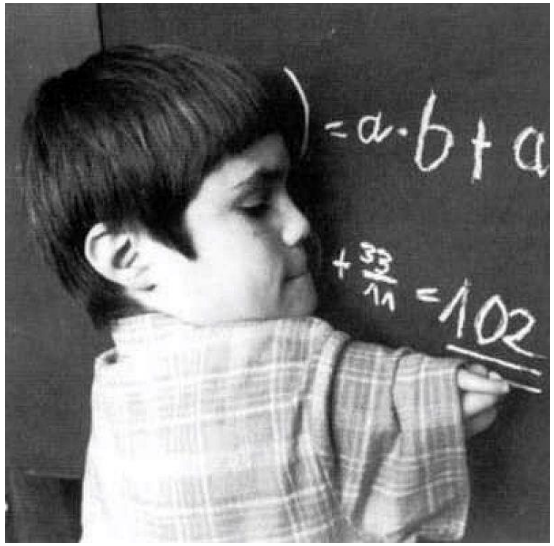
In the US, rubella infection during one year has caused more malformations (Cooper, ’68) than thalidomide over whole marketing period (Schardein, ’93)





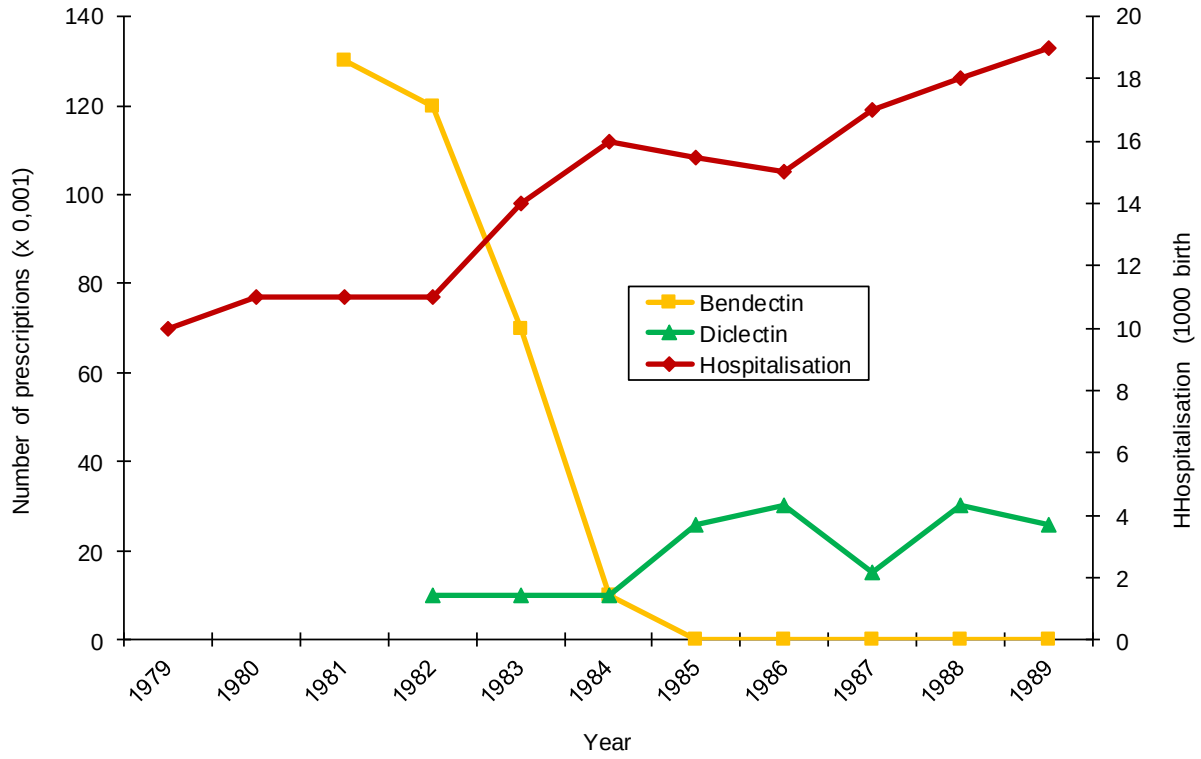
Thalidomide catastrophe





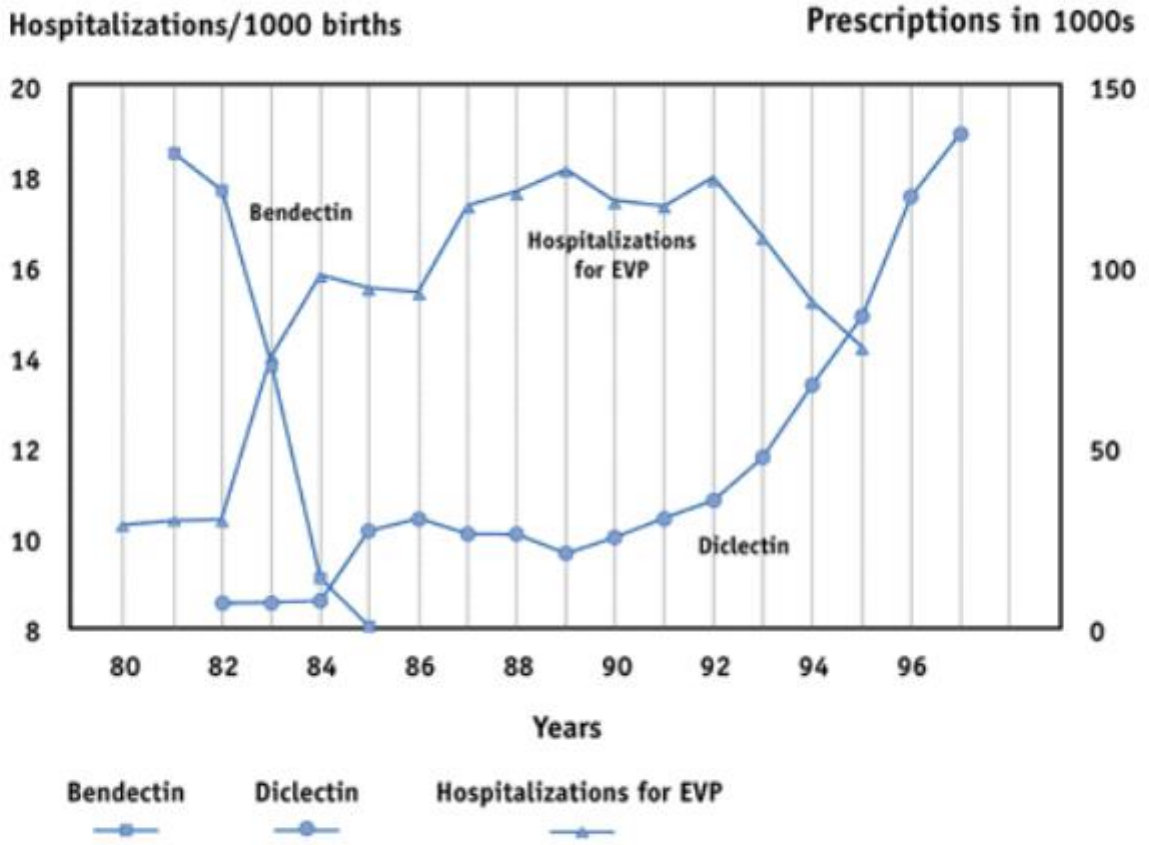
Frances Oldham Kelsey received the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy, 1962

“Bendectin” story (doxylamine+pyridoxine)



NEJM 1998;338:1128-1137

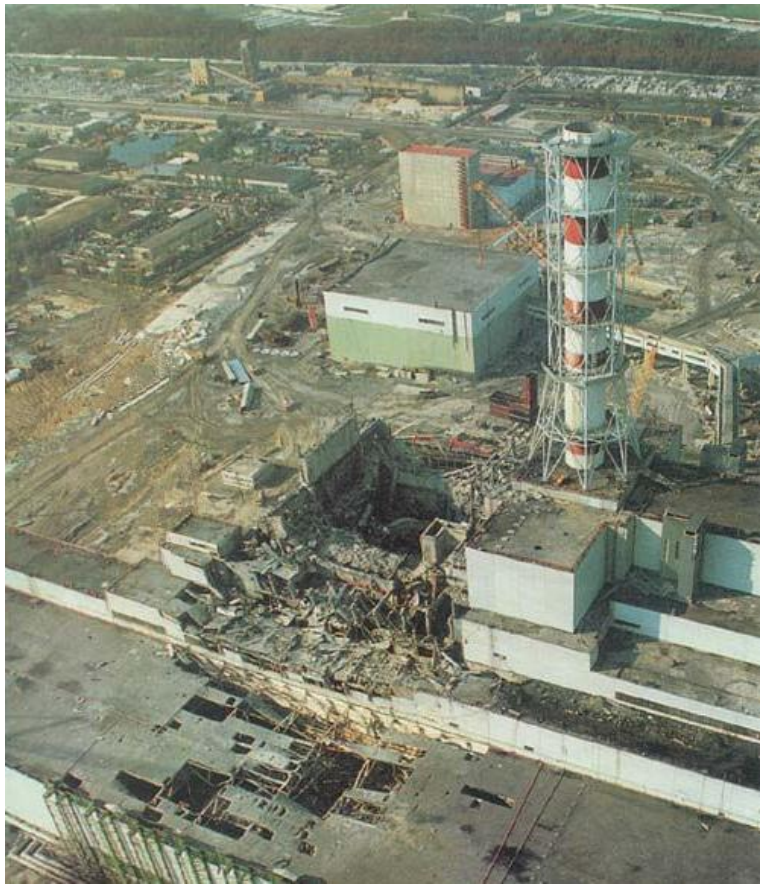
FIGURE 1 - HOSPITALIZATIONS FOR EXCESSIVE VOMITING IN PREGNANCY (EVP) AND BENDECTIN/DICLECTIN USE* IN CANADA



*Canadian Compuscript, 1981-1997. Quoted by permission.

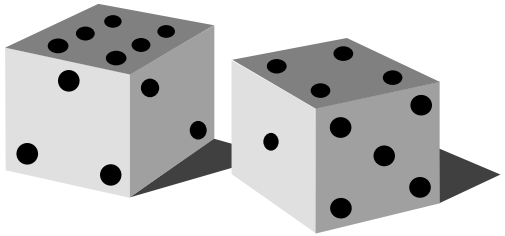
Neutel CI, Variation in rates of hospitalization for excessive vomiting in pregnancy by Bendectin/Diclectin use in Canada, *Nausea and Vomiting of Pregnancy : State of the Art 2000*, Toronto, The Motherisk Program, 2000;54-9

Chernobyl catastrophe



- Termination of many pregnancies due to Chernobyl accident in Greece

- Congenital malformations (birth defects) – irreversible functional or morphological defects, manifested at birth
- Causes
  - Genetic factors
  - Environmental factors
    - Medicines
    - Chemicals
    - Radiation
    - Pathogens
    - Maternal illness
  - Combinations



- Teratogen is an exogenous factor that can cause congenital malformations during embryonic or fetal development

- Major malformations (2–4%)
- Minor malformations
- The frequency of malformations caused by environmental factors is 0.1–0.2%

Principles of Teratogenesis (1)

- Toxin exposure time (″probability window″)
  - some teratogens cause malformations only during a certain period of development
  - Coumarin derivatives – 6–9 weeks.
  - Thalidomide – 20–22 days – ear malformations; 28–33 d. – limb malformations
  - Carbamazepine – 0–7 days – nervous tube defects
  - After 10 weeks teratogen does not cause major defects other than of brain
- Dose dependence

Principles of Teratogenesis (2)

- Interspecies variation
  - Xenobiotics have different effects on different species of animals
  - Coumarins are teratogenic only to humans
  - Aspirin is teratogenic to most animal species, but not to humans
- Congenital malformations may vary from one species to another

Criteria for evaluation of teratogenicity (according to Shepard)

1. Confirmed exposure of the agent during a critical period (appointment by a doctor, prescription, other data)
2. Relevant findings from 2 or more qualitative epidemiological studies
3. Accurate and consistent clinical case description (specific defect or syndrome)
4. Rare environmental factors are associated with rare defects (such as oral anticoagulants and nasal hypoplasia, methylases and scalp defects)
5. Teratogenicity in animals is important, but not essential
6. The association must have a biological plausibility
7. Experimental confirmation is important for protection

- Clinical trials are never performed in pregnant women to evaluate an effect on fetus
- Therefore, many medicines are not recommended for use during pregnancy
- Or “The use in pregnancy is not recommended unless the expected benefit to the mother exceeds the potential damage to the fetus“

Pregnancy calender

Gestational age (weeks)	Embryonic age (days after conception)	Survivals, %	Chance to survive before birth, %
2	0–6	100	50
4	7–13		
5	14–20	71	70
6–7	21–35	57–63	79–88
8–9	36–49	55	90
10	50–56	51	98
34–40		50	

Avery's Drug Treatment 1997

Embryonic and fetal development

- Blastogenesis (0–2 weeks "all or nothing")
- Embryogenesis (3–8 weeks – rapid development of all organs. During this period, the embryo is most sensitive to teratogenic effects)
- Fetogenesis (from week 9 – rapid growth and differentiation of organs)

Embryonic and fetal pharmacokinetics

- Fetal drug distribution
  - More water, less fat – higher volume of distribution of water soluble substances
- Embryonic and fetal drug metabolism
  - Are able to metabolise xenobiotics in any phase of development
  - Hepatic metabolism starts at week 7–8.
    - I and II phase
    - cytochromo P450 enzyme concentration at week 11–18 becomes similar to adults, lower activity
    - Glucuronisation – inadequate, sulphation – quite good

Identification of teratogen

- Animal models
- Case reports (base for investigation)
- Case-control studies
- Cohort studies
- Registries
- Interventional studies (folic acid and neural tube defects)
- Meta-analyses

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors

William O. Cooper, M.D., M.P.H., Sonia Hernandez-Diaz, M.D., Dr.P.H., Patrick G. Arbogast, Ph.D., Judith A. Dudley, B.S., Shannon Dyer, B.S., Patricia S. Gideon, R.N., Kathi Hall, B.S., and Wayne A. Ray, Ph.D.

N Engl J Med 2006;354:2443-51.

Table 2. Risk of Major Congenital Malformations among Study Infants According to Fetal Exposure to Antihypertensive Medications during the First Trimester Alone.*

Variable	ACE Inhibitor (N=209)	Other Antihypertensive Medication (N=202)	No Antihypertensive Medication (N=29,096)†
Any congenital malformation			
No. of infants	18	4	834
Percentage of births	7.12	1.73	2.63
Risk ratio	2.71	0.66	1
95% confidence interval	1.72–4.27	0.25–1.75	Reference
Cardiovascular malformation			
No. of infants	9	2	294
Percentage of births	2.90	0.70	0.78
Risk ratio	3.72	0.89	1
95% confidence interval	1.89–7.30	0.22–3.59	Reference
Central nervous system malformation			
No. of infants	3	0	80
Percentage of births	1.46	0	0.33
Risk ratio	4.39	—	1
95% confidence interval	1.37–14.02	—	Reference
Other malformations			
No. of infants	6	2	469
Percentage of births	2.71	0.95	1.55
Risk ratio	1.75	0.62	1
95% confidence interval	0.79–3.89	0.15–2.45	Reference

* Infants could have both cardiovascular and central nervous system malformations and be included in these groups; the other malformations group included only infants without cardiovascular or central nervous system malformations. The proportions and risk ratios are adjusted for potential confounders. Models include maternal age, race, presence or absence of a chronic illness, rural or urban residence, and income quartile and the year of the child's birth. The estimation accounts for clustering due to a woman with either multiple pregnancies during the study period or a multiple-gestation pregnancy.

† Infants in this group had no fetal exposure to antihypertensive medications.

As indications for ACE inhibitors have expanded,[2,34] their use among women of childbearing age has increased. Data from the National Ambulatory Medical Care Survey show that between 1995 and 2002 the use of ACE inhibitors in female patients 15 through 44 years of age increased by 83 percent (from 2.4 percent to 4.4 percent).[35] This increase in use is likely to result in an increase in first-trimester fetal exposures. Our data suggest that such exposures cannot be considered safe and should be avoided.

4.3 Contra-indications

- Hypersensitivity to the ACE inhibitor prescribed or any other ACE inhibitor.
- History of angioneurotic oedema associated with previous ACE inhibitor therapy
- Hereditary/idiopathic angioneurotic oedema
- Pregnancy
- Lactation period.

4.6 Pregnancy and lactation

Appropriate and well-controlled studies have not been done in humans. ACE inhibitors cross the placenta and can cause foetal and neonatal morbidity and mortality when administered to pregnant women.

Foetal exposure to ACE inhibitors during the second and third trimesters has been associated with neonatal hypotension, renal failure, face or skull deformities and/or death. Maternal oligohydramnios has also been reported reflecting decreasing renal function in the foetus. Limb contractures, craniofacial deformities, hypoplastic lung development and intrauterine growth retardation have been reported in association with oligohydramnios. Infants exposed *in utero* to ACE inhibitors should be closely observed for hypotension, oliguria and hyperkalemia. Oliguria should be treated with support of blood pressure and renal perfusion.

Intrauterine growth retardation, prematurity, patent ductus arteriosus and foetal death have also been reported but it is not clear whether they are related to the ACE inhibition or the underlying maternal disease.

It is not known whether exposure limited to the first trimester can adversely affect foetal outcome. Women who become pregnant while receiving an ACE inhibitor should be informed of the potential hazard to the foetus.

SSRI use during pregnancy

Objective To investigate any association between selective serotonin reuptake inhibitors (SSRIs) taken during pregnancy and congenital major malformations.
Design Population based cohort study.
Participants 493 113 children born in Denmark, 1996-2003.

Conclusion There is an increased prevalence of septal heart defects among children whose mothers were prescribed an SSRI in early pregnancy, particularly sertraline and citalopram. The largest association was found for children of women who redeemed prescriptions for more than one type of SSRI.

Table 2 | Odds ratios for malformations according to two or more prescriptions for individual selective serotonin reuptake inhibitors (SSRIs)*

Birth defects	No of unexposed infants (n=493 113)	Fluoxetine (n=348)		Citalopram (n=460)		Paroxetine (n=299)		Sertraline (n=259)		More than one type of SSRI (n=193)	
		No of infants	OR† (95% CI)	No of infants	OR† (95% CI)	No of infants	OR† (95% CI)	No of infants	OR† (95% CI)	No of infants	OR† (95% CI)
Minor malformations	7373	4	0.62 (0.20 to 1.93)	7	0.79 (0.33 to 1.91)	6	1.43 (0.64 to 3.22)	3	0.76 (0.24 to 2.37)	4	1.08 (0.34 to 3.38)
Major malformations	15 518	11	1.00 (0.53 to 1.88)	17	1.07 (0.63 to 1.83)	15	1.41 (0.79 to 2.51)	12	1.51 (0.84 to 2.69)	10	1.62 (0.83 to 3.16)
Cardiac malformations	3988	2	0.77 (0.19 to 3.11)	6	1.75 (0.78 to 3.93)	3	0.88 (0.22 to 3.55)	5	2.36 (0.97 to 5.72)	5	3.42 (1.40 to 8.34)
Septal heart defects	2315	2	1.34 (0.33 to 5.41)	5	2.52 (1.04 to 6.10)	1	0.76 (0.11 to 5.43	4	3.25 (1.21 to 8.75)	4	4.70 (1.74 to 12.7)
Non-cardiac malformations	11 530	9	1.08 (0.54 to 2.19)	11	0.83 (0.41 to 1.67)	12	1.59 (0.85 to 2.99)	7	1.18 (0.56 to 2.50)	5	0.95 (0.35 to 2.57)

*Four women used fluvoxamine only with no recorded malformations.
†Adjusted for age, calendar year, income, marriage status, tobacco smoking.

BMJ 2009;339:b3569

Birth Defects Research (Part A) 73:906–918 (2005)

Nongenital Malformations Following Exposure to Progestational Drugs: The Last Chapter of an Erroneous Allegation

Robert L. Brent*
Research Department, Alfred I. duPont Hospital for Children, Wilmington, Delaware

Received 31 August 2004; Revised 17 May 2005; Accepted 1 June 2005

Progestogens “proof of innocence”

1930-1960	Sex hormones are widely used; feminization, masculinisation
1967-1976	Case studies: Nongenital disorder: acquired cardiac defects, nerve tube defects, limb defects, VACTERL (vertebral, anal, cardiac, T-E fistula, renal, rib, limbs) association (uncertainty due to drug use recall bias)
1977	Intervention and evaluation time. Quite controversial research publications. Based on the results of some studies, the FDA has added a warning to the progestin and contraceptives leaflet of the more common cardiac and limb malformations
1977-1987	Many epidemiological studies are performed (most big cohort studies). Most of them do not support the relationship between hormones and birth defects. Prospective studies. Analysis of previously obtained data. Causal relationship is not proved
1988	The FDA has removed a warning from a leaflet on oral contraceptives about possible association with birth defects
1988-1999	It took another 11 years before the warning for non-genital birth defects was removed from all progestogen leaflets.

Birth Defects Research (Part A): Clinical and Molecular Teratology 73:906–918 (2005)

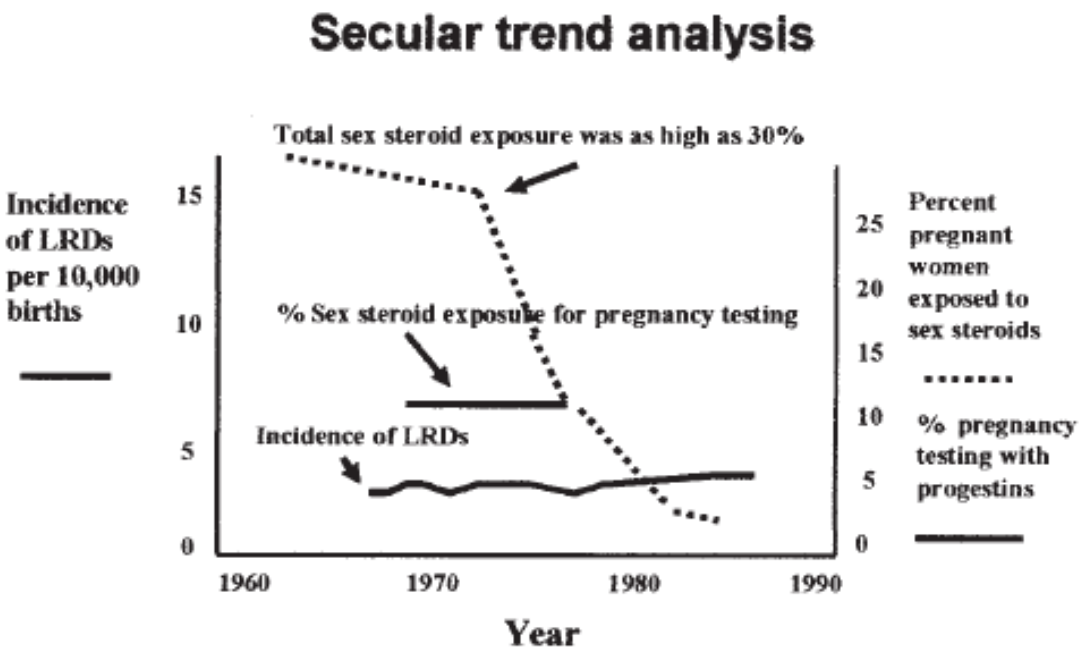


Figure 1. The graph contains 3 sets of data. The first pertains to the incidence of LRDs during the 1970s and 1980s. The second set describes the extent of the use of sex steroids during the 1970s and 1980s. The third set describes the use of progestins (primarily medroxyprogesterone) as a pregnancy test prior to the development of immunological pregnancy tests. Although the incidence of LRDs increased only slightly during this period, there was a dramatic drop in the exposure of pregnant women to sex steroids following the FDA warning in 1977. Because a substantial percentage of pregnant women received progestins, secular trends in the malformations and exposures do not support an association between progestin exposure and the occurrence of LRDs.

The epidemiologic analyses, animal studies, and basic science principles have been reviewed, and it is obvious that clinically utilized progestational drugs do not cause nongenital malformations (i.e., LRDs and CHDs). *Birth Defects Research (Part A) 73:906–918, 2005.*

Medicines – human teratogens (1)

Medicine	Effect
Aminopterin, methotrexate	CNS and limbs malformations
ACE inhibitors	Long–term neonatal renal failure, abnormal skull ossification, renal tubular dysgenesis
Anticholinergic medicines	Newborn meconium ileus
Anti–thyroid medicines	Fetal and neonatal hyperthyroidism and hypothyroidism, aplasia cutis (metamizole)
Carbamazepine	Nervous tube defects
Cyclophosphamide	CNS defects, secondary tumors
Danazole and other androgens	Masculinisation of a female fetus
Diethylstilbestrol	Vaginal carcinoma and other urogenital defects
Hypoglycemic agents	Neonatal hypoglycemia
Lithium	Epstein syndrome
Misoprostol	Mobius syndrome

Koern g. et al. NEJM 1998

Medicines – human teratogens (2)

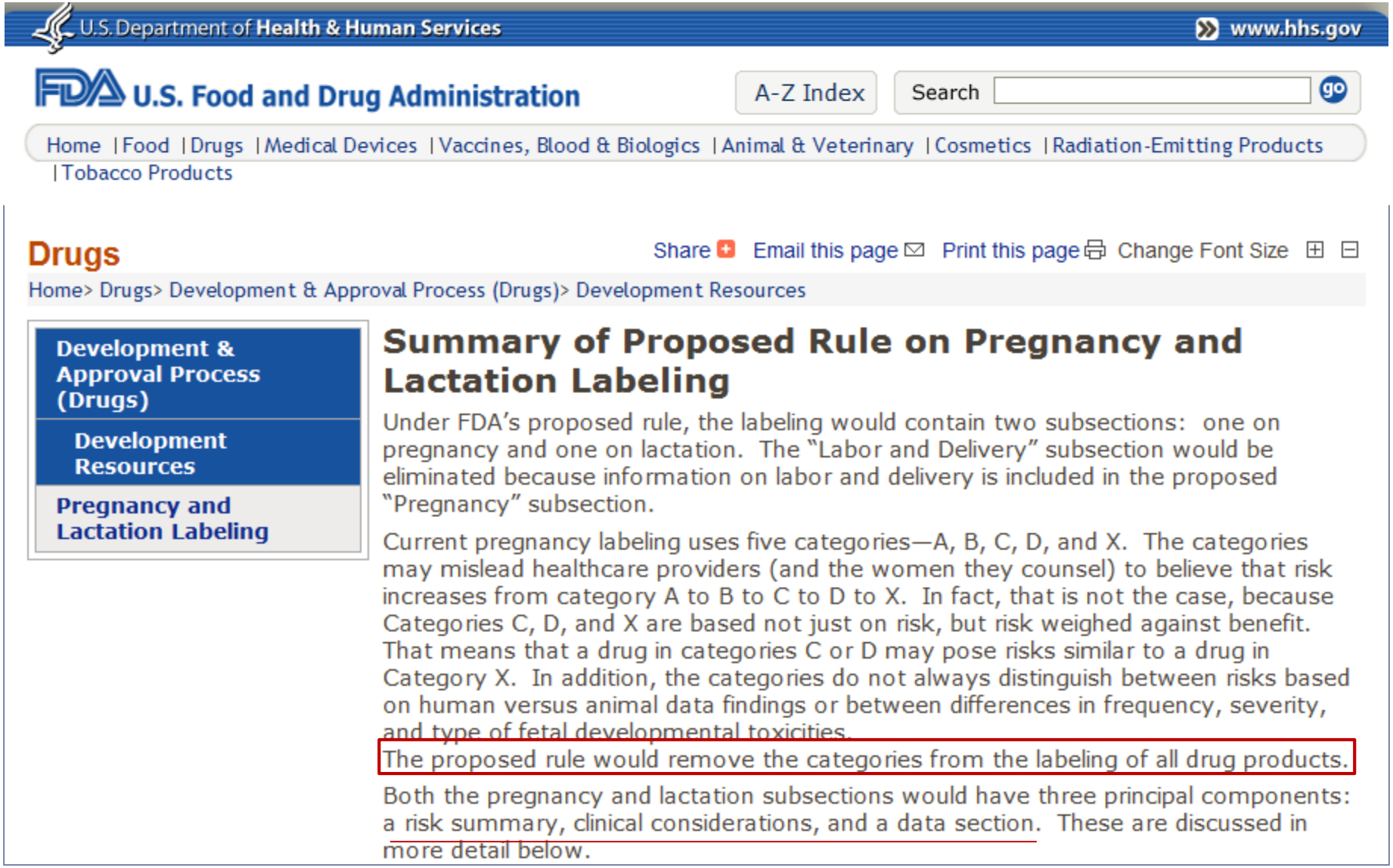
Medicine	Teratogenic effect
NSAIDs	Arterial duct constriction, necrotizing enterocolitis
Parametadione	Face and CNS defects
Phenytoin	growth retardation, CNS defects
Psychotropics (barbiturates, opioids, benzodiazepines)	Neonatal withdrawal syndrome
Systemic retinoids	CNS, craniofacial, cardiovascular defecs
Tetracycline	Tooth and bone anomalies
Thalidomide	Focomelia, other malformations
Trimethadione	Face and CNS defects
Valproate	Nervous tube defects, other birth defects, autism spectrum disorders, mental disorders, ADHS
Warfarin	Skeletal and CNS defects, Dandy–Walker syndrome

Koern g. et al. NEJM 1998

Medicines whose teratogenicity has been denied

Medicine	Suspected malformations	Evidence of safety
Diazepam	Lip and palate defects	Risks do not increase in large-group and case-control studies
COC	Congenital spine, anus, heart, trachea, esophageal, kidney and limb defects; pseudohermafroditism	Two meta-analyzes did not reveal any association between the use of oral contraceptives in the I trimester and these malformations
Spermicides	Limb defects, tumors, Down syndrome, hypospadias	Meta-analysis did not reveal an increased risk
Salicylates	Palate defects and congenital heart disease	In large group studies, the risk was not increased
Bendectin	Heart and limb defects	Two meta-analysis did not reveal an increased risk

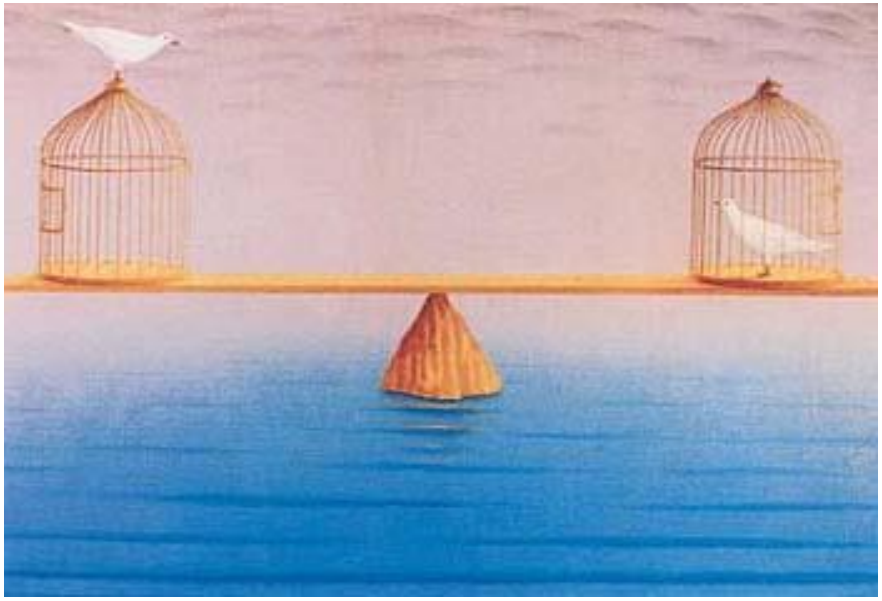
Koern g. et al. NEJM 1998



Page Last Updated: 04/30/2009

Principles of prescribing drugs for pregnant women

- Benefit–risk ratio
- Consideration before going to get pregnant
- Considering unplanned pregnancy
- Retrospective evaluation of the role of teratogen
- Informed choice

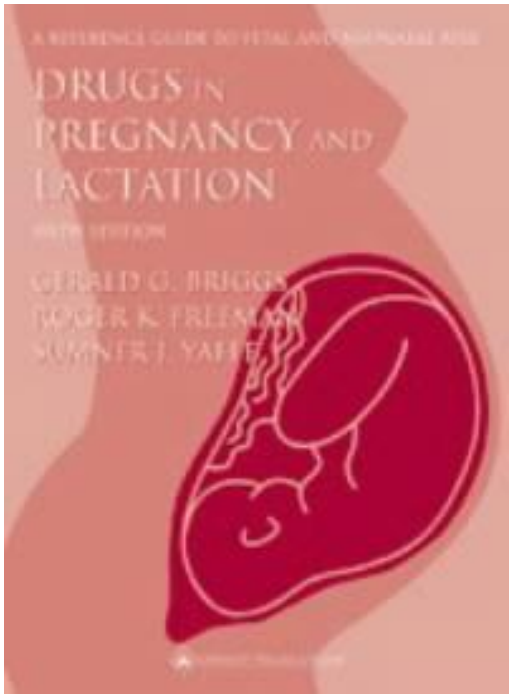


- During pregnancy, the mother and the fetus form a unified system
- The mother's well-being is a prerequisite for the optimal functioning and development of both units
- If necessary, the mother should be adequately treated considering the effect on the fetus

https://youtu.be/CzeJSzkrygM

Information

- http://www.motherisk.org
- http://www.otispregnancy.org
- http://cerhr.niehs.nih.gov



- Drug use and lactation

Risk assessment

- Excretion of drug to the milk
  - drug properties (plasma protein binding, ionization, lipophilicity, molecular weight)
  - kinetics in the mother's body
  - Ratio of concentration of the drug in milk and plasma
- Level of exposure

- The drug is safe when the infant receives no more than 10% of the therapeutic dose with milk; or when the exposure index is <10%
- Exceptions are the lack of G6PD

www.thelancet.com Vol 368 August 19, 2006

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of diffi culty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis showed no anatomical anomalies. Blood concentration of morphine (the active metabolite of codeine) was 70 ng/mL by gas chromatography-mass spectrometry (GC-MS)—neonates breastfed by mothers receiving codeine typically have morphine serum concentrations of 0–2·2 ng/mL.1

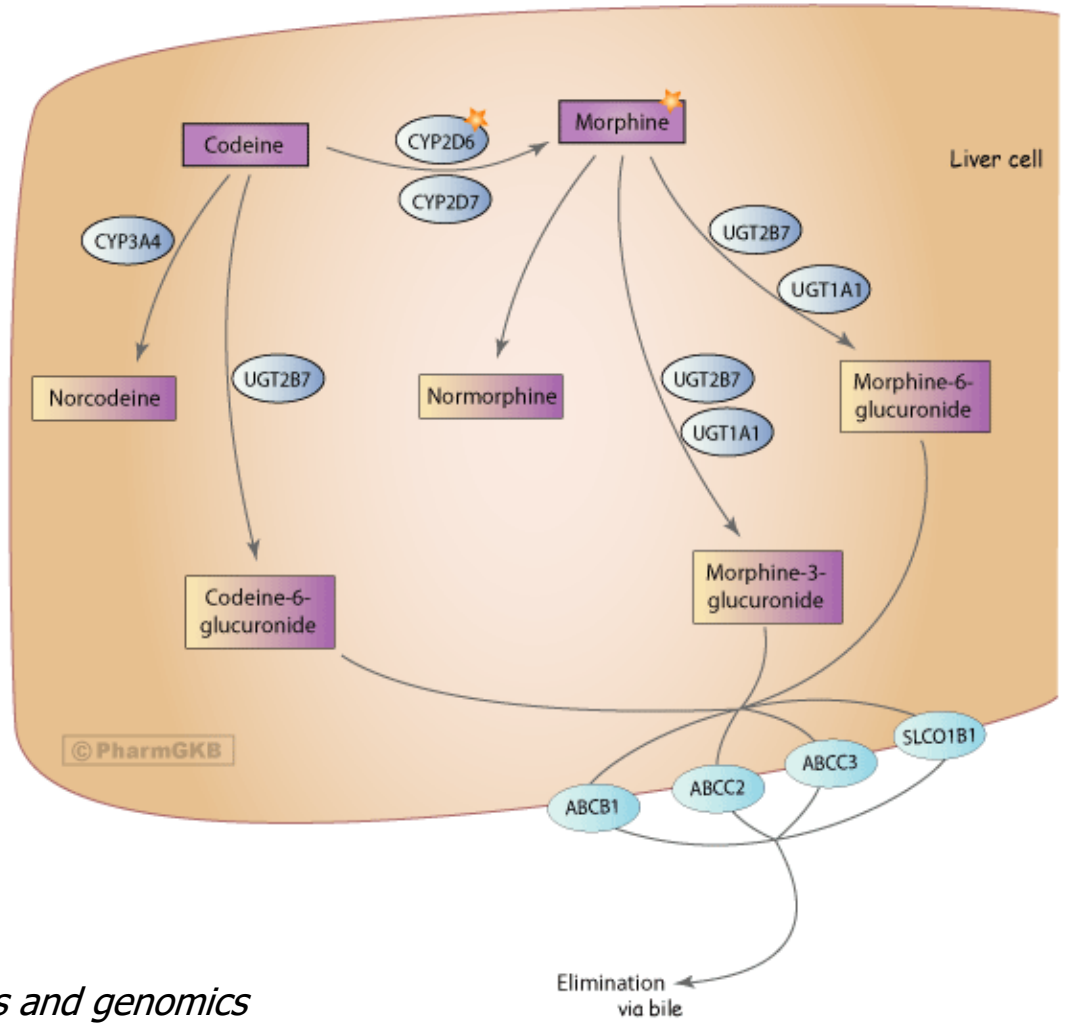
Case Report

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

The mother had been prescribed a combination preparation of codeine 30 mg and paracetamol 500 mg after birth for episiotomy pain (initially two tablets every 12 h, reduced to half that dose from day 2 because of somnolence and constipation). She continued the tablets for 2 weeks. Because of poor neonatal feeding, she stored milk on day 10, which was later assayed for morphine by GC-MS. A morphine concentration of 87 ng/mL was found—the typical range of milk concentrations after repeated maternal codeine is 1·9–20·5 ng/mL at doses of 60 mg every 6 h.

Codeine metabolism



Caroline TF et al. Pharmacogenetics and genomics (2009)

Genotyping

Genotype analysis was done for cytochrome P450 2D6 (CYP2D6), the enzyme catalysing the O-demethylation of codeine to morphine.2 The mother was heterozygous for a CYP2D6*2A allele with CYP2D6*2×2 gene duplication, classifi ed as an ultra-rapid metaboliser. This genotype leads to increased formation of morphine from codeine, consistent with the somnolence and constipation she experienced.3 The maternal grandfather, the father, and the infant had two functional CYP2D6 alleles (CYP2D6*1/*2 genotypes), classifi ed as extensive metabolisers. The maternal grandmother was an ultra-rapid metaboliser.

Medicines whose benefits and risks need to be evaluated

Class of medicines	Medicines
Analgetikai	Meperidinas, oksikodonas, kodeinas
Antiartritiniai vaistai	Aukso druskos, metotreksatas, didelės aspirino dozės
Antikoaguliantai	Fenindionas
Antidepresantai ir litis	Fluoksetinas, doksepinas, litis
Antiepilepsiniai vaistai	Fenobarbitalis, etosukcimidas, primidonas
Antimikrobiniai vaistai	Chloramfenikolis, tetraciklinai
Priešvėžiniais vaistai	Visi
Anksiolitikai	Diazepamas, alprazolamas
Kardiovaskuliniai ir antihipertenziniai vaistai	Acebutalolis, amiodaronas, atenololis, nadololis, satololis
Endokrininę sistemą veikiantys vaistai	Estrogenai, bromokriptinas
Imunosupresantai	Ciklosporinas, azatioprinas
Kvėpavimo sistemą veikiantys vaistai	Teofilinas
Radioaktyvūs preparatai	Visi
Priklausomybę sukeliantys vaistai	Visi
Kitos medžiagos	Etanolis, kofeinas, nikotinas, jodas ir jo preparatai, ergotaminas, ergonovinas

Medicines, that may be used during breast feeding

Class of medicines	Medicines
Analgetikai	Acetaminofenas, ibuprofenas, ketorolakas, sumatriptanas, morfinas
Antikoaguliantai	Varfarinas, acenokumarolis, heparinas
Antidepresantai	Sertralinas, TCA
Antiepilepsiniai vaistai	Karbamazepinas, fenitoinas, valproinė rūgštis
Antihistamininiai vaistai	Loratadinas
Antimikrobiniai vaistai	Penicilinai, cefalosporinai, aminoglikozidai, makrolidai
Beta adrenoblokatoriai	Labetalolis, propranololis
Endokrininę sistemą veikiantys vaistai	Propiltiouracilis, insulinas, levotiroksinas
Gliukokortikoidai	Prednizolonas, prednizonas